

How Does HIV Persist and What Can We Do About It?

Demystifying Medicine

January 30th, 2018

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2 in 1: Persistence of HIV Both Globally and Individually

Part 1: Global Persistence of HIV

Case History

“Suffering, no matter how vast in number, is always individual”

Summary of global HIV epidemic (2016)

Number of people living with HIV in 2016

Total	36.7 million [30.8 million – 42.9 million]
Adults	34.5 million [28.8 million – 40.2 million]
Women	17.8 million [15.4 million – 20.3 million]
Men	16.7 million [14.0 million – 19.5 million]
Children (<15 years)	2.1 million [1.7 million – 2.6 million]

People newly infected with HIV in 2016

Total	1.8 million [1.6 million – 2.1 million]
Adults	1.7 million [1.4 million – 1.9 million]
Children (<15 years)	160 000 [100 000 – 220 000]

AIDS deaths in 2016

Total	1.0 million [830 000 – 1.2 million]
Adults	890 000 [740 000 – 1.1 million]
Children (<15 years)	120 000 [79 000 – 160 000]

Source: UNAIDS/WHO estimates.

HIV CAN BE TRANSMITTED THROUGH...



**Sexual
Contact**



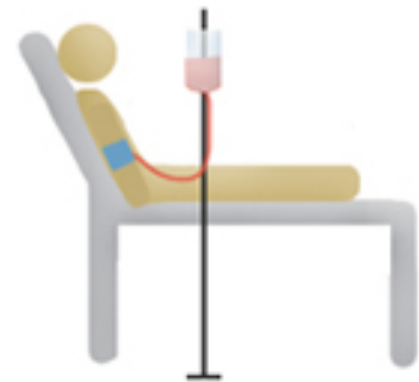
**Pregnancy, Childbirth
& Breast Feeding**



**Injection
Drug Use**



**Occupational
Exposure**



**and rarely,
Blood Transfusion/Organ Transplant**

ABCs of Stopping HIV Transmission

A. Reduce infectivity of infected individuals

- **Antiretroviral therapy!**

- Cohort studies, HPTN 052 (90+ % reduction)

- HIV cure, if possible (see later)

B. Eliminate contact with HIV

- Possible for blood supply

- Not possible for sexual transmission

C. Reduce susceptibility of uninfected individuals

- **Male circumcision!** (50-60% reduction)

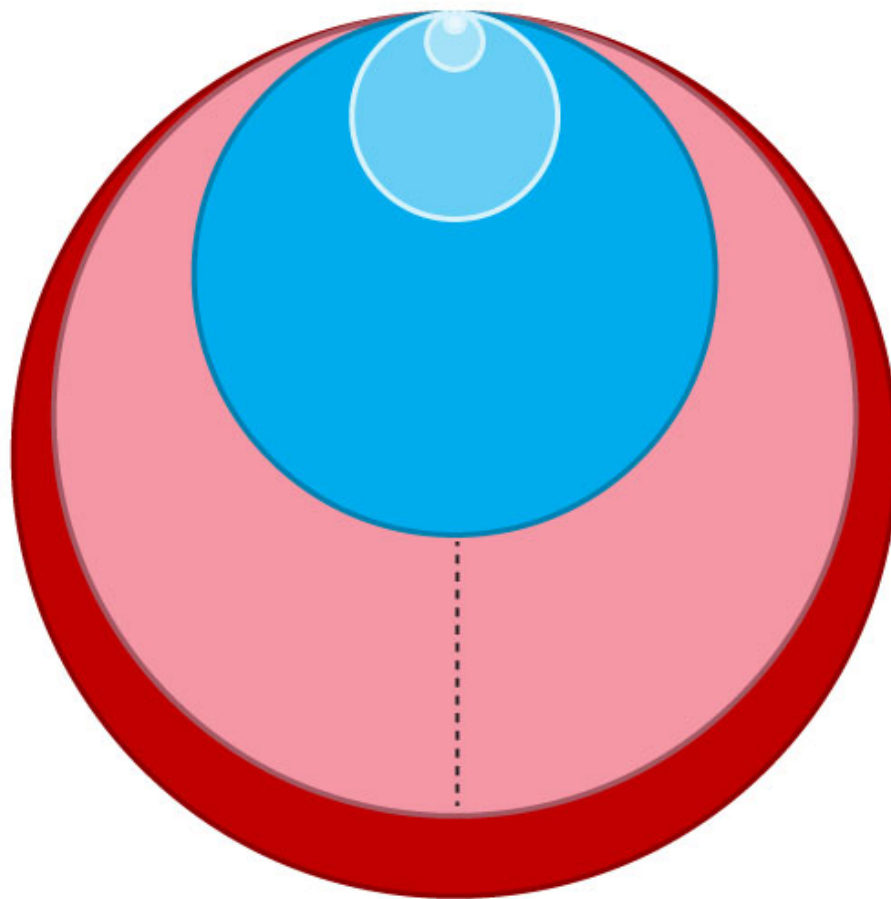
- Chemo prophylaxis = **PrEP!** (Pre-exposure Prophylaxis)

- Vaccine prophylaxis...

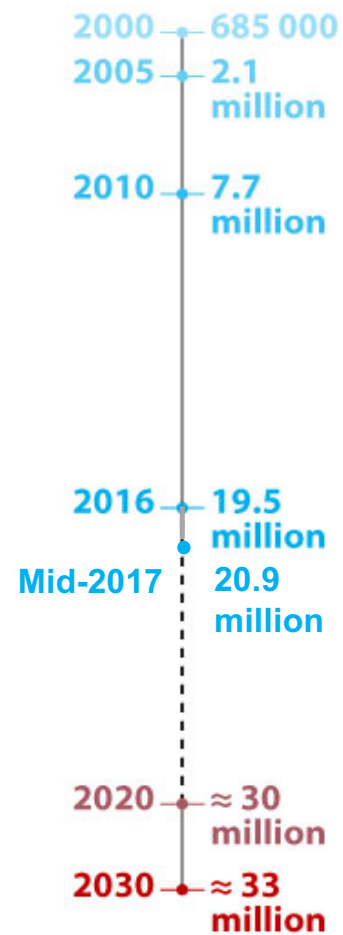
Progress In HIV Prevention

- ART Rollout is impacting transmission
 - Incidence declining in several African countries
- PrEP works, if taken
 - IPrEx and multiple other studies
 - “On Demand” PrEP makes sense & works (IPERGAY)
- More people are taking PrEP
 - Especially in the US; national rollouts starting: Kenya
- Resistance from PrEP is infrequent
 - Mostly when started in acute HIV infection
 - Rare breakthroughs are being reported
- But, other STIs are on the rise (41% incidence in IPERGAY)
 - Increase in condomless sex
- Better PrEP is coming and needed for the youth bulge!
 - Topical, longer acting oral, injectable, implantable

Number of people receiving antiretroviral treatment



UNAIDS/WHO estimates

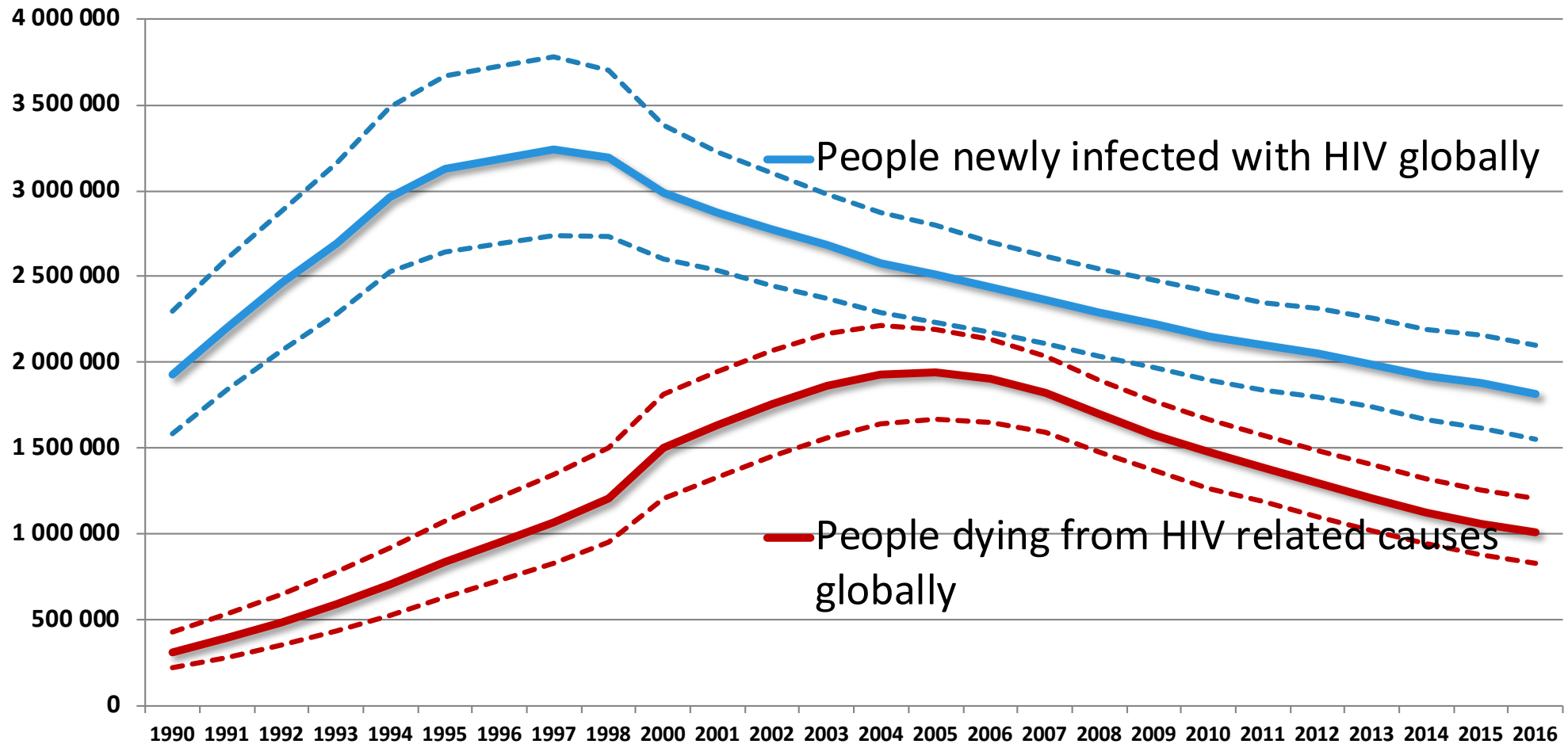


Future targets



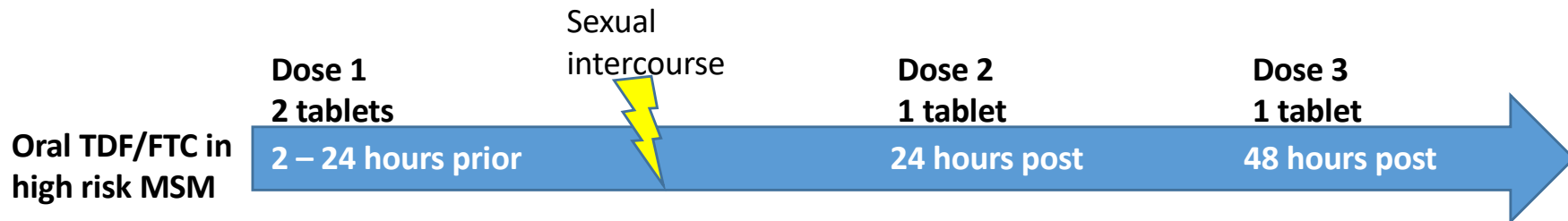
World Health Organization

Decline in HIV incidence and mortality over time



Source: UNAIDS/WHO estimates.

High Efficacy of Open-Label, On-Demand PrEP



IPEGAY phase	Person-years of follow-up	Incidence of HIV Infection per 100 person-years [95% CI]
IPEGAY double-blinded (Placebo Arm)	212	6.60 [3.61-11.07]
IPEGAY double-blinded (TDF-FTC Arm)	219	0.91 [0.11-3.30]
IPEGAY open phase (open-label TDF-FTC)	248	0.40 [0.01-2.25]

TDF/FTC PrEP Resistance Occurs Infrequently in Seroconverters

Seroconverted on TDF/FTC Arm during follow-up

Study	Seroconverters in TDF/FTC Arm	TFV Resistance		FTC Resistance	
		Standard	Sensitive	Standard	Sensitive
FEM-PrEP	33	0	0	4	1
iPrEX	36	0	0	0	2
TDF2	9	0	0	0	0
Partners PrEP	21	0	1	0	5
VOICE	61	0	0	1	2
TOTAL	160	0 (0%)	1 (0.6%)	5 (3%)	10 (6%)

**How will
HIV drug
resistance
from PrEP be
monitored and
prevented?**



**GEMS provides a comprehensive
assessment of HIV drug resistance
risk with PrEP use and policy
recommendations for the frequency
of HIV testing and resistance
monitoring for projects implementing
PrEP in sub-Saharan Africa.**

Find out more at gems.pitt.edu or contact gems@pitt.edu



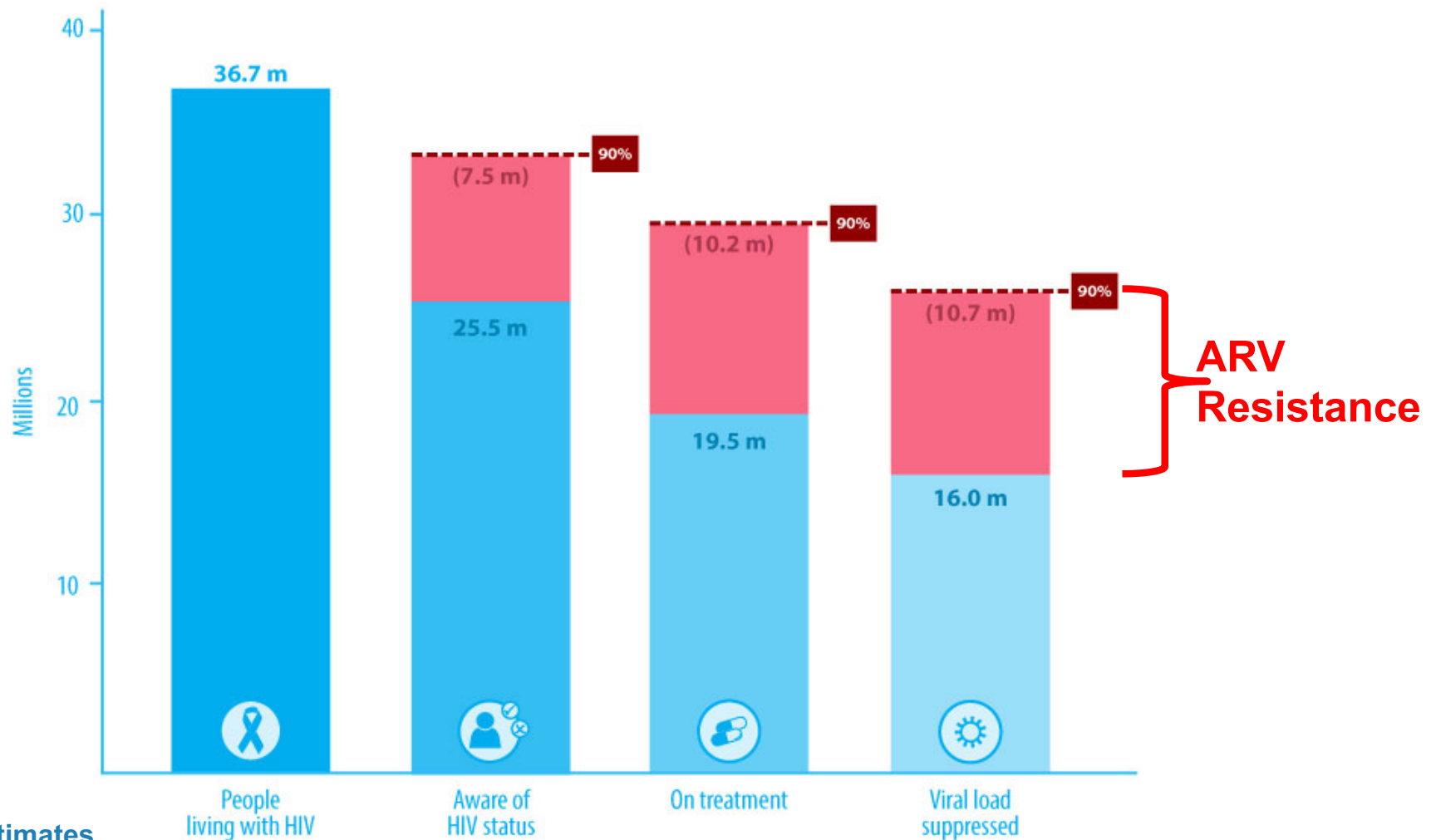
USAID
FROM THE AMERICAN PEOPLE



GEMS partners include FHI 360, BARC-Lancet Laboratories, University College London and University of Washington/Fred Hutchinson Cancer Research Center.

Threats to HIV Prevention

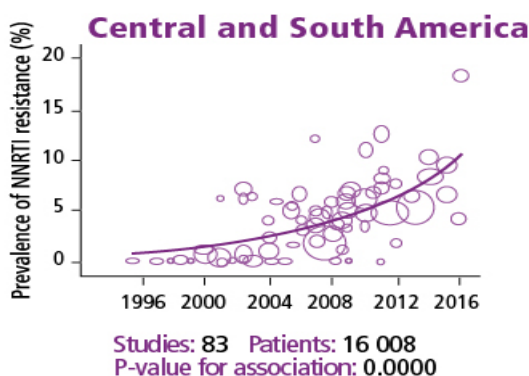
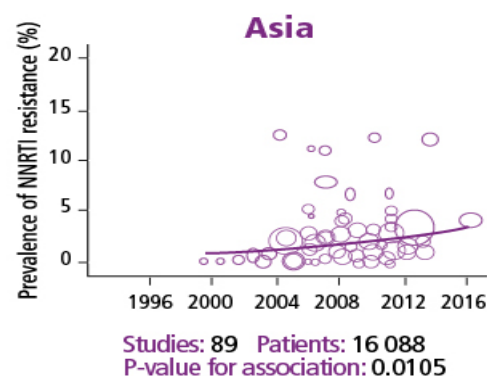
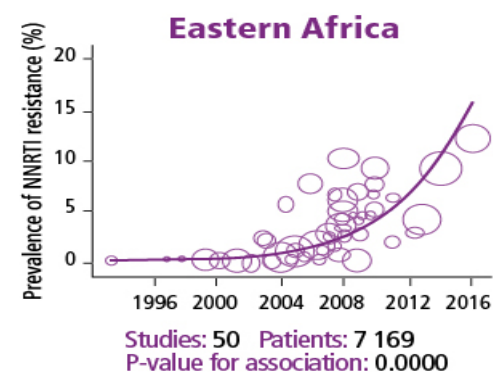
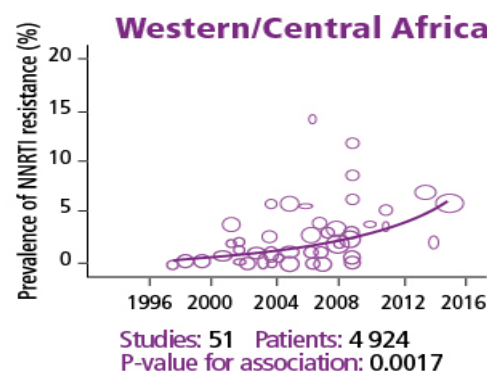
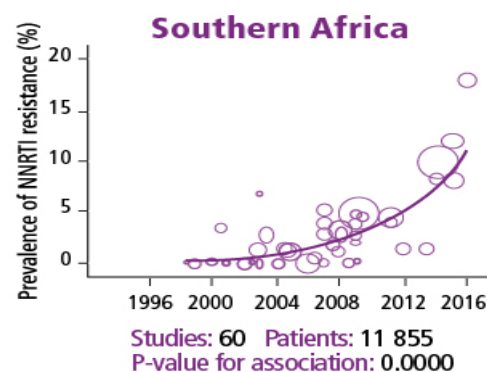
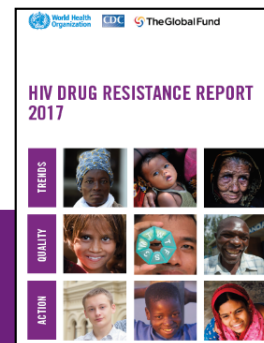
HIV testing and care continuum (2016)



Nachega, et al. Achieving viral suppression in 90%. Clin Inf Dis 2018

The Emerging Threat of HIV Drug Resistance

Prevalence of NNRTI pre-treatment resistance by calendar year (systematic review)



— Fitted line

Source: *Report on HIV drug resistance 2017*. Geneva: World Health Organization; 2017

Solution?

Tenofovir/Lamivudine/Dolutegravir (TLD)

- Better tolerated and higher efficacy than efavirenz based regimens, i.e., TLE
- Little to no transmitted dolutegravir (DTG) resistance
- PEPFAR rollout starting (\$75 per year!)
 - 1st line
 - 2nd line
 - Beyond...
- **Cautions:**
 - DTG monotherapy can select resistance
 - TL components overlap with TLE and TNV/FTC for PrEP
 - Double dosing of DTG required with rifampin (Tb)

PrEP Breakthrough Cases

Multidrug-Resistant HIV-1 Infection Despite Adherence to PrEP

- Background
 - Patient: 43 y/o man on oral TDF/FTC in Toronto
 - Reported condomless sex 2 to 6 weeks prior to HIV Ab/Ag detection
- HIV and drug level testing
 - 7 NR 4th gen screening tests up to 21 months after PrEP start
 - Day 0: Ab/Ag pos., WB neg.; Detectable Plasma TDF
 - Day 7: Ab pos; Ag neg; WB neg.
 - **Day 24: DBS TFV-DP conc. consistent with long-term adherence**
- Genotype/Phenotype (Day7)
 - Standard and deep sequencing
 - NRTI: 41L, 67G, 69D, 70R, 184V, 215E
 - NNRTI: 181C
 - Phenotyping
 - **Resistant to: 3TC/FTC, nevirapine**
- Conclusions
 - Multiple TAMs are unlikely to have been selected due to short duration of PrEP exposure after HIV acquisition.
 - **Incident HIV is possible despite adherence to PrEP**

Pipeline of New PrEP

- Dapivirine Intravaginal Ring (DPV IVR)
 - Under EMA review
- FTC/Tenofovir alafenamide (F/TAF)
 - In Phase III
- Rilpivirine LA (RPV LA)
 - Development stopped: cross-resistance
- Cabotegravir LA (CBV LA)
 - In Phase III
- **EFdA (MK-8591)**
 - **Once weekly dosing protects macaques**
- **Capsid Inhibitor (GS-CA1)**
 - **Preclinical, low pMolar potency, long-term depot delivery possible?**

Ending Global Persistence of HIV?

- Massive rollout of simpler, safer, non-overlapping and longer-acting ART and PrEP that will require:
 - New drugs and drug delivery systems
 - Stronger public health infrastructure
 - National leadership and cooperation!
 - Resources
 - Monitoring capacity
 - Human persistence

Questions?

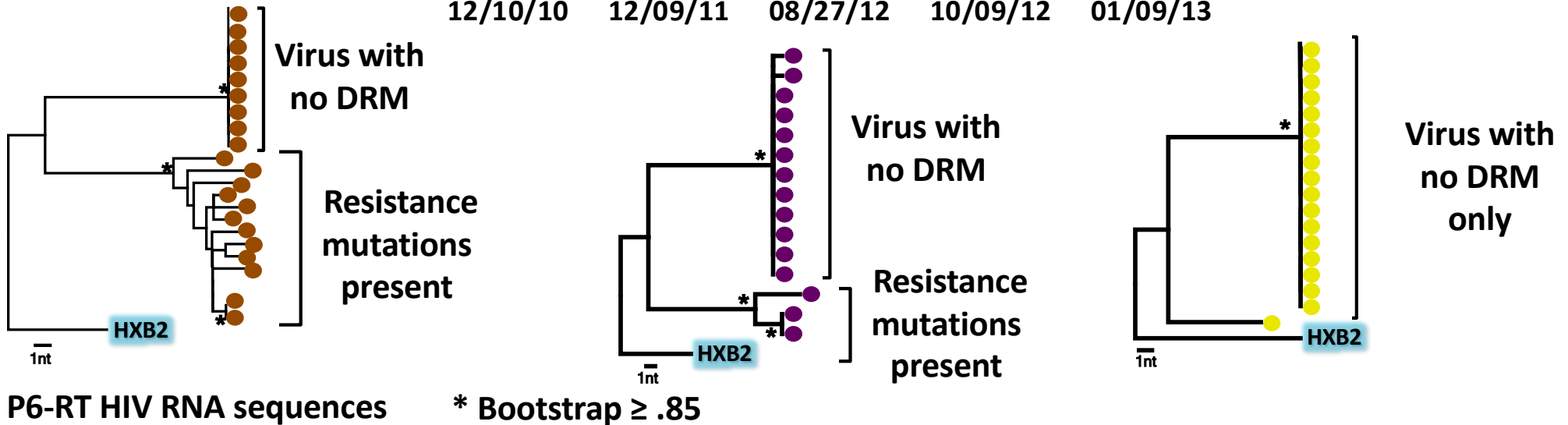
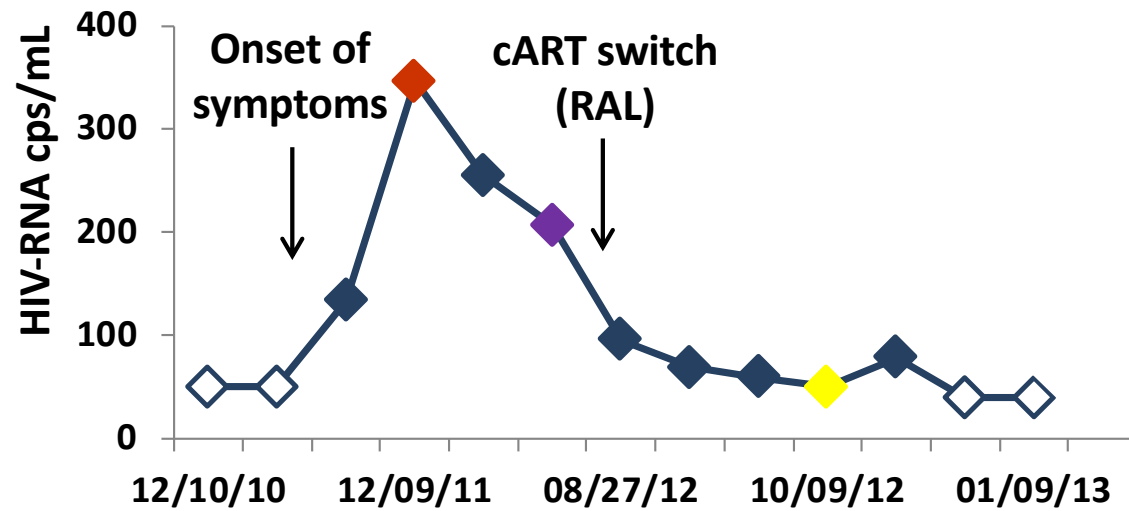
Part 2: Persistence of HIV in An Individual

A Case of non-suppressible “wildtype” viremia

- 58 y.o. AA man diagnosed with HIV-1 in 2000
 - Initial CD4+T-cell 16
 - HIV-1 RNA 283,000 copies/ml
 - cART started, HIV-1 RNA < 50 copies/ml w/i 4 mos
- After 12 years, HIV-1 RNA increased to 200 copies/ml
 - Diagnosed with SCC of tongue
- cART switched, viremia persisted ~ 100 copies/ml
 - Single genome sequencing analysis performed

Simonetti, et al. PNAS 2016

Persistent Viremia Following Onset of Squamous Cell Carcinoma

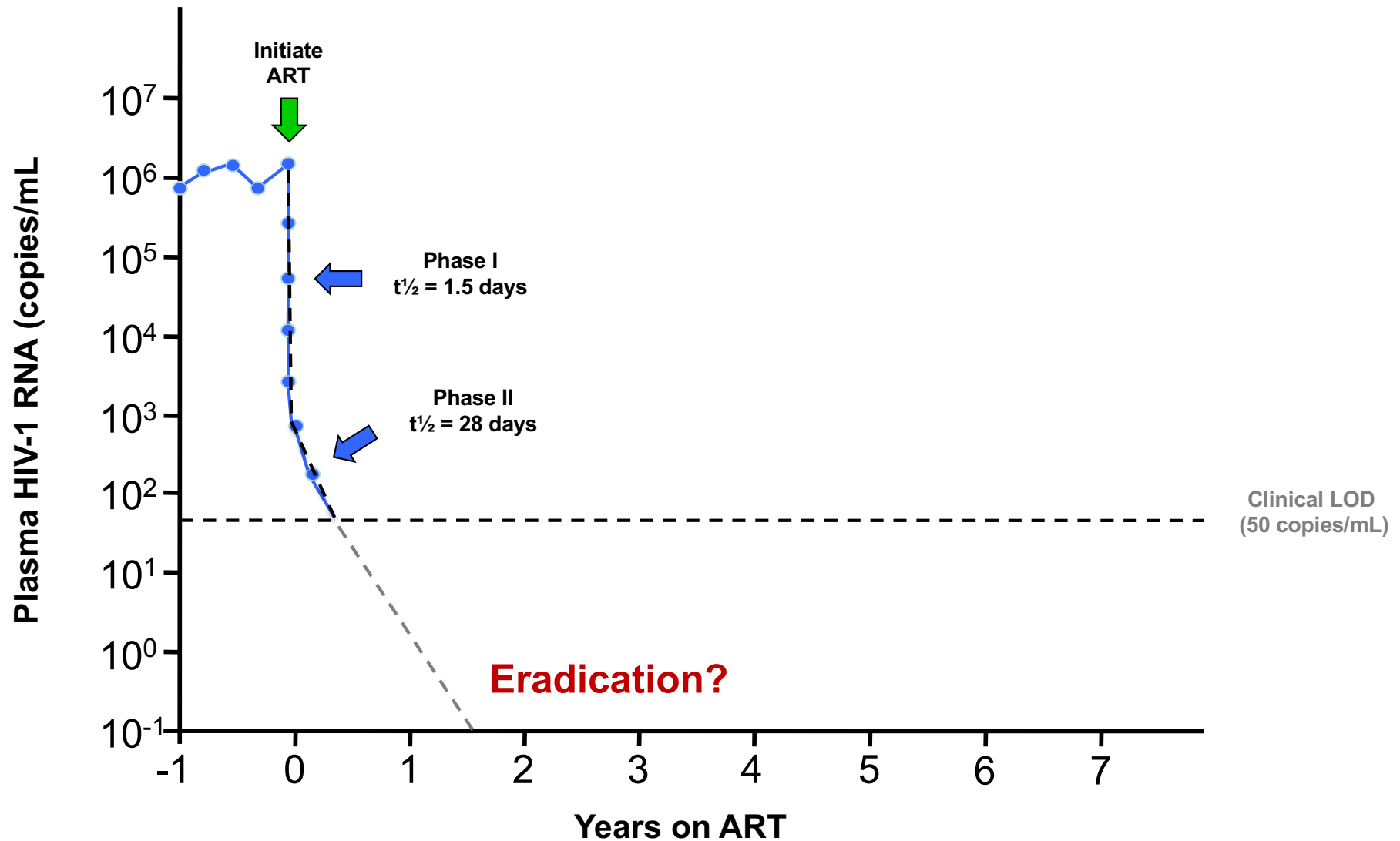


Simonetti, et al. PNAS 2016

HIV Cure Strategies

A Short History of HIV Cure Research

1996-7: HIV Cure Possible?



HIV Cure “Impossible”: 1997-2009

SCIENCE VOL. 278 * 14 NOVEMBER 1997

Identification of a Reservoir for HIV-1 in Patients on Highly Active Antiretroviral Therapy

Diana Finzi, Monika Hermankova, Theodore Pierson, Lucy M. Carruth, Christopher Buck, Richard E. Chaisson, Thomas C. Quinn, Karen Chadwick, Joseph Margolick, Ronald Brookmeyer, Joel Gallant, Martin Markowitz, David D. Ho, Douglas D. Richman, Robert F. Siliciano*

Recovery of Replication-Competent HIV Despite Prolonged Suppression of Plasma Viremia

Joseph K. Wong,* Marjan Hezareh, Huldrych F. Günthard, Diane V. Havlir, Caroline C. Ignacio, Celsa A. Spina, Douglas D. Richman

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 13193–13197, November 1997
Medical Sciences

Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy

TAE-WOOK CHUN*[†], LIEVEN STUYVER[‡], STEPHANIE B. MIZELL*, LINDA A. EHLE*^{*}, JO ANN M. MICAN*, MICHAEL BASELER[§], ALUN L. LLOYD[¶], MARTIN A. NOWAK[¶], AND ANTHONY S. FAUCI*

Latent HIV Reservoir Discovered in Resting CD4+T-cells

BRIEF REPORT

Long-Term Control of HIV by CCR5 Delta32/ Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S.,
Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D.,
Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D.,
Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D.,
and Eckhard Thiel, M.D.

SUMMARY

Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the CCR5 allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for CCR5 delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role CCR5 plays in maintaining HIV-1 infection.

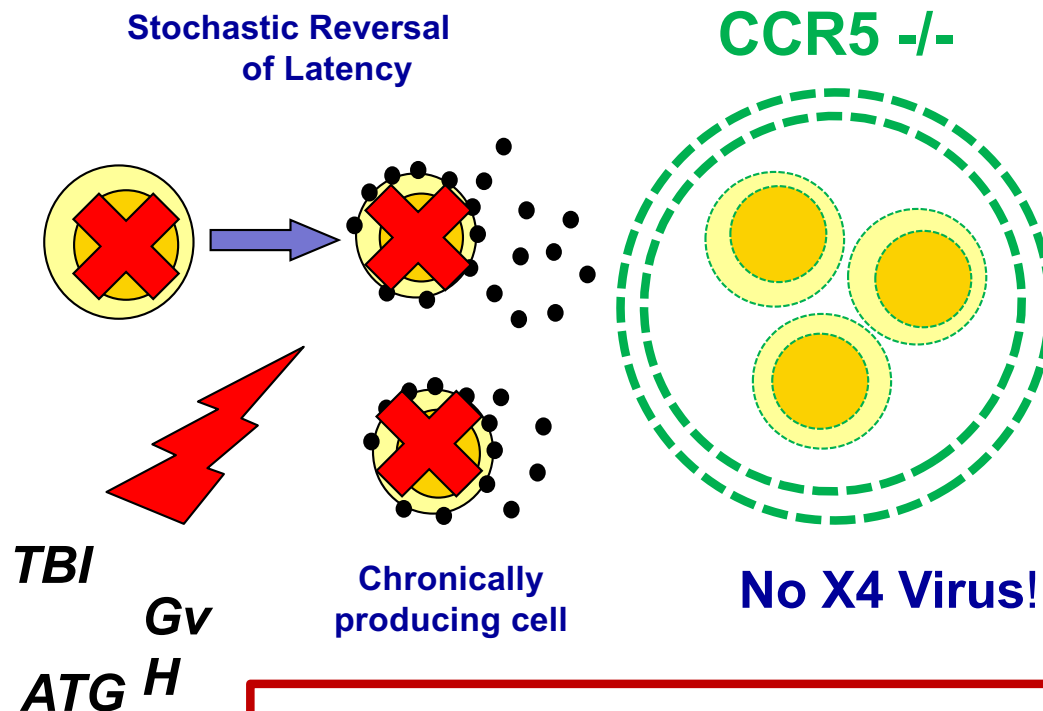
N Engl J Med. 2009; 360:692-8



**Timothy Ray Brown,
The American in 'Berlin
Patient'**

No HIV Detectable After Many Years

How was Tim Brown Cured?



Mortality from Allogeneic BMT ~ 25%

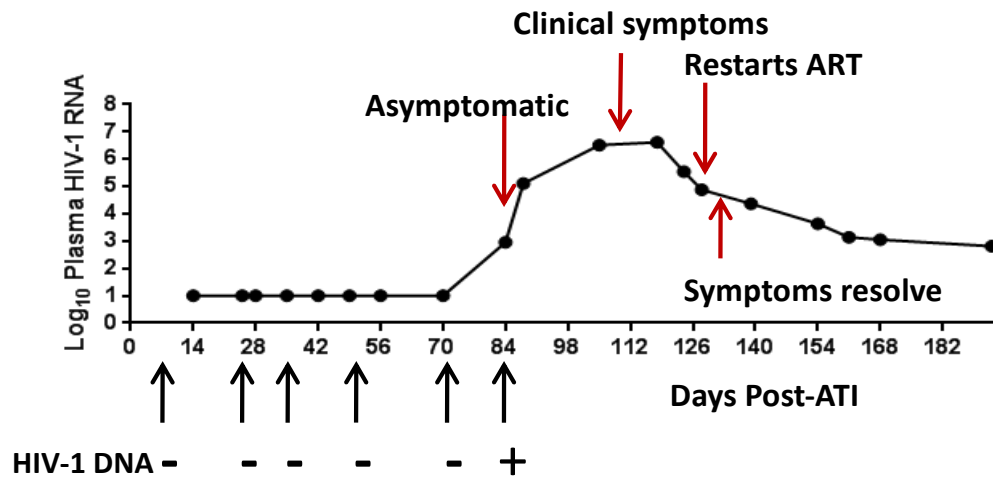
Primarily inspirational!



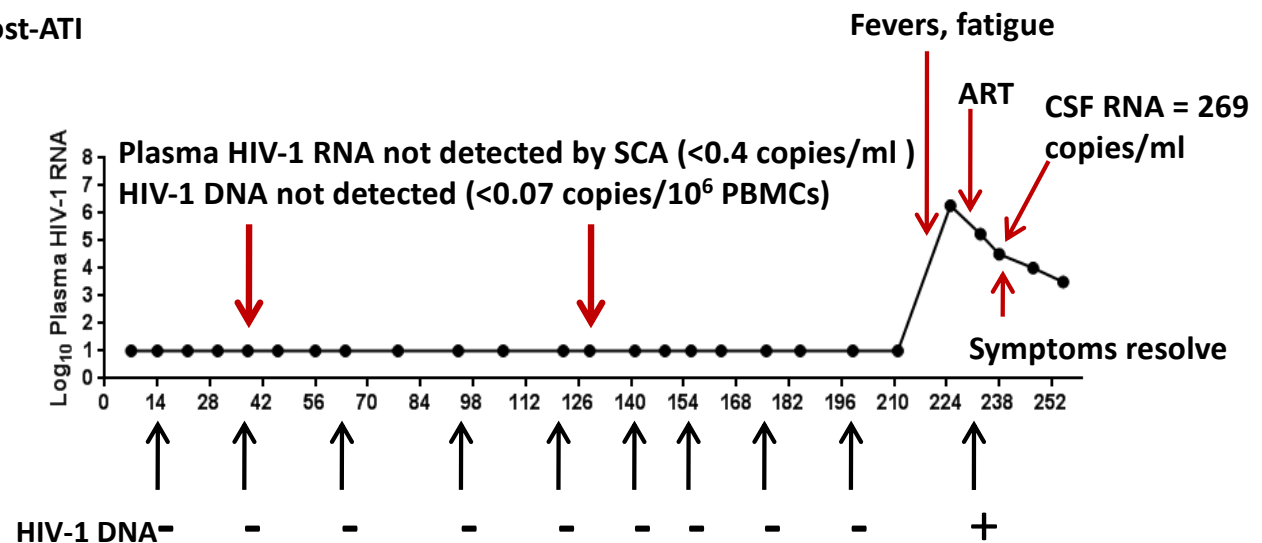
Boston Allotransplants (Henrich et al., Ann Intern Med 2014)

HSCT/Patient Factor	Patient A	Patient B
Mode of acquisition	Perinatal	Sexual (adult)
CCR5 genetics	$\Delta 32$ Heterozygous	$\Delta 32$ Heterozygous
Favorable HLA alleles?	No	No
Pre-HSCT HIV-1 DNA	144 copies/ 10^6 PBMC	96 copies/ 10^6 PBMC
Type of Allogeneic HSCT	HLA C-mismatched unrelated; CCR5^{wt/wt}	Matched related donor; CCR5^{wt/wt}
HSCT Conditioning	Reduced intensity	Reduced intensity
GVHD	Chronic, mild (skin)	Chronic, mild (skin)
Length of ART post-HSCT	4.5 years	2.8 years
Blood Chimerism	<0.001% host PBMC	<0.001% host PBMC
Post-HSCT HIV-1 DNA	undetectable	undetectable

Patient A: ART Stopped



Patient B: ART Stopped



No other Cures from Allo-transplants with CCR5^{-/-} donors

Table 1. Men with Human Immunodeficiency Virus Type 1 (HIV-1) Infection Who Received an Allogeneic Transplant from a Stem-Cell Donor Who Was Homozygous for the CCR5 delta32/delta32 Mutation.*

Location of Transplantation	Age of Patient yr	Type of Cancer	Type of Graft	Outcome after Transplantation
Berlin†	40	Acute myeloid leukemia	HLA-matched unrelated	Alive after 7 yr, no viral rebound, no ART
Utrecht, the Netherlands‡	53	Myelodysplastic syndrome	Combined haploidentical bridge with umbilical-cord blood	Died from relapse of the myelodysplastic syndrome and pneumonia after 2 mo
Münster, Germany§	51	Non-Hodgkin's lymphoma	HLA-mismatched unrelated	Died from infection after 4 mo
Essen, Germany¶	30	Non-Hodgkin's lymphoma	HLA-matched unrelated	CXCR4-tropic HIV-1 rebound, died from relapse of non-Hodgkin's lymphoma after 12 mo
Minneapolis§	12	Acute lymphoblastic leukemia	Umbilical-cord blood	Died from GVHD after 3 mo
Santiago, Chile§	46	Non-Hodgkin's lymphoma	HLA-matched related	Died from pneumonia shortly afterward
Barcelona§	37	Non-Hodgkin's lymphoma	Combined haploidentical bridge with umbilical-cord blood	Died from relapse of non-Hodgkin's lymphoma after 3 mo

**100%
Mortality**

Hütter, NEJM 2015

Eradication Cure?



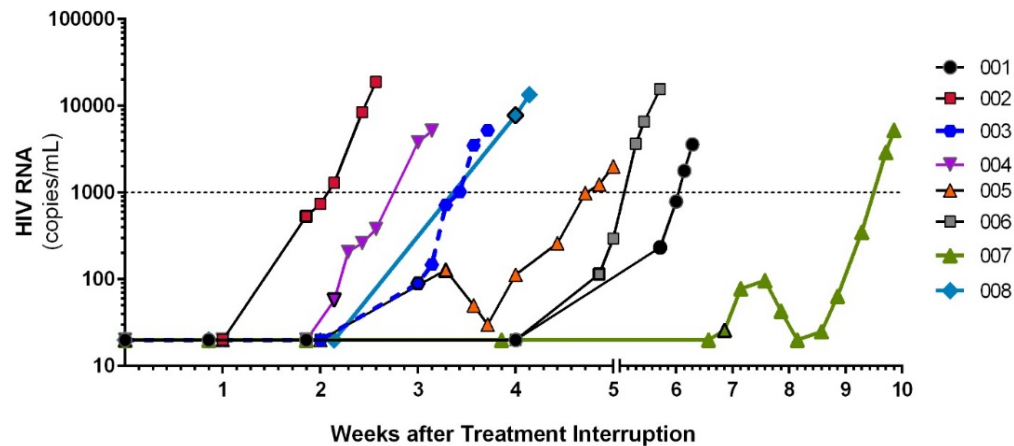
Early ART Is Not Early Enough

RV₄₁₁: Time to VL Rebound in Fiebig I Treated Individuals

7 men and 1 woman
median age 29 yrs
ART in Fiebig I for median of 2.8 yrs
VL < 20, no blips
Median CD4 577 cells/mm³



ATI for up to 24 weeks
(VL q 3-7 days)
ART resumed with VL > 1000



Time to viral load rebound >20 copies/ml
Median 26 days
Range 13 to 48 days

Colby, Ananworanich et al, 2017 CROI

Which Cure Strategy?



Host Modification

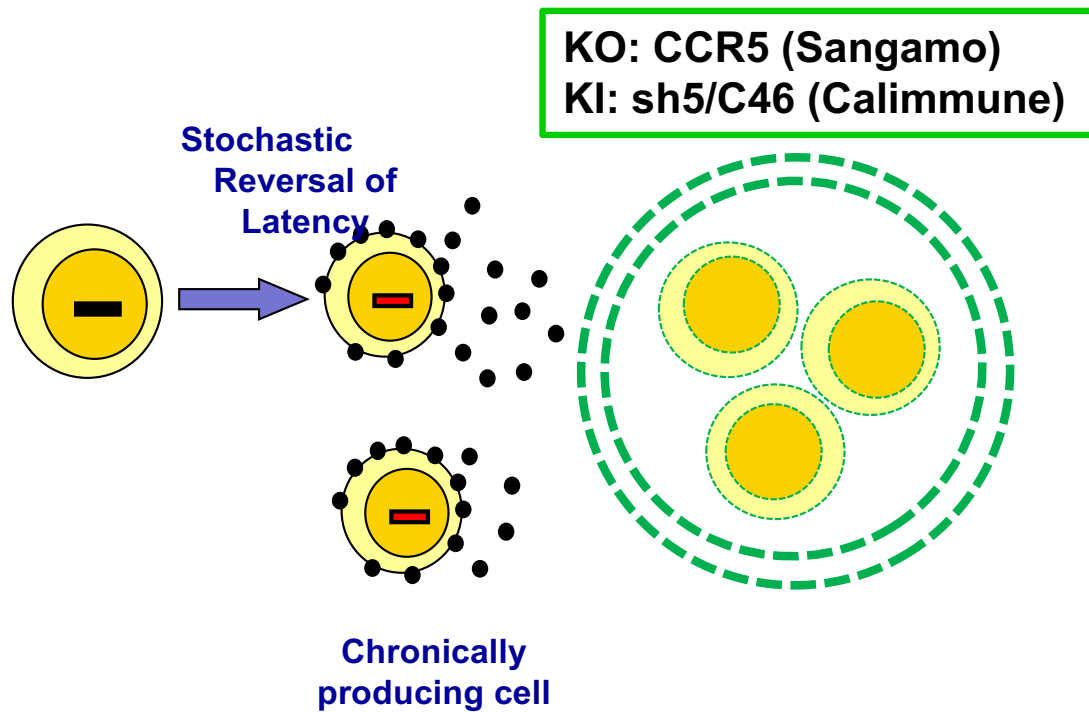
Confer resistance of
susceptible cells to HIV



Kick and Kill

Reduce reservoirs &
improve immune control
without ART

Host cell modification



The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

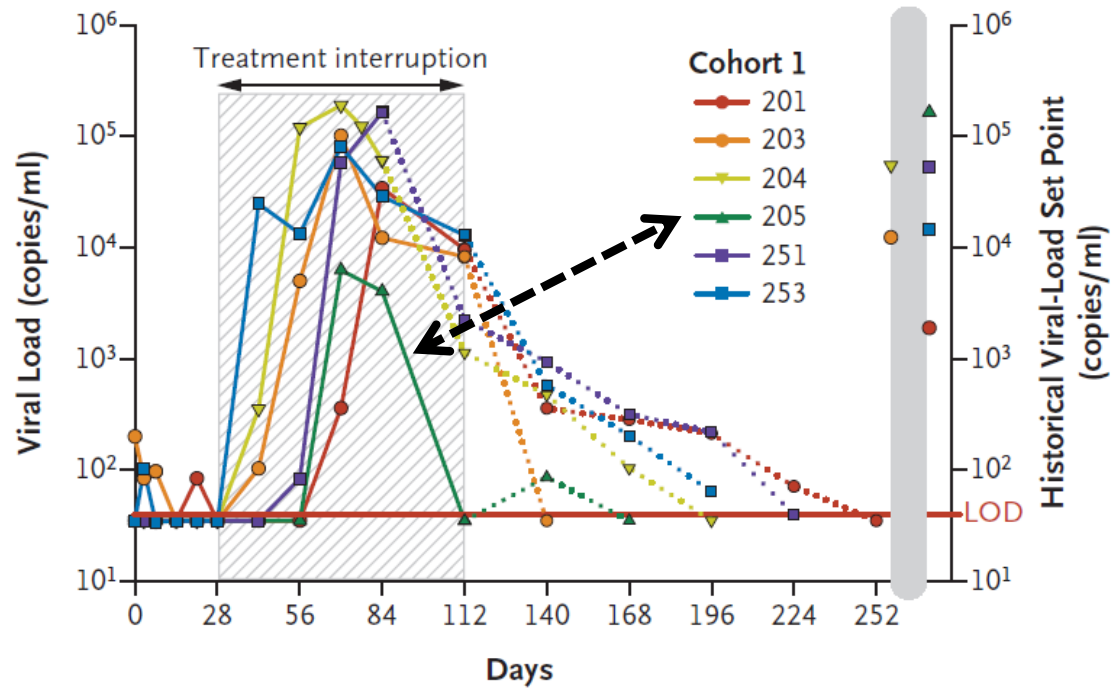
MARCH 6, 2014

VOL. 370 NO. 10

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

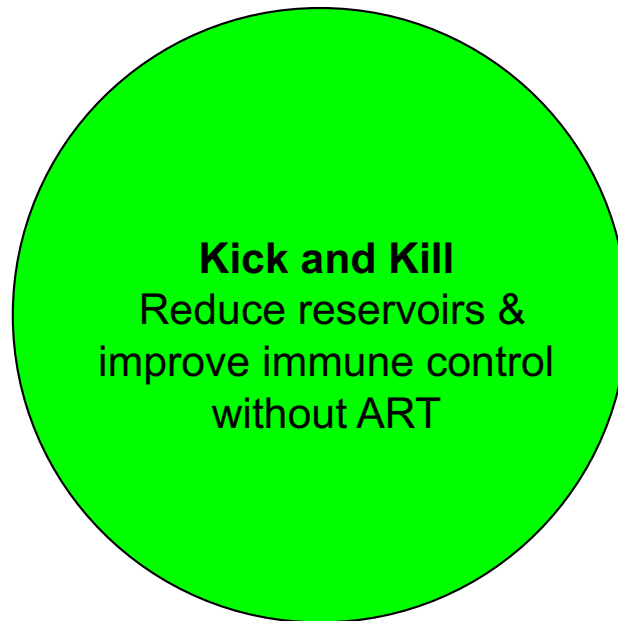
Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D.,
S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D.,
Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D.,
Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D.,
Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

- CCR5-modified CD4 T cells at 1 week post infusion constituted 13.9% of circulating CD4 T cells
- Modified cells had an estimated mean half-life of 48 weeks
- After ART interruption, decline in circulating CCR5-modified cells (-1.81 cells per day) was significantly less than the decline in unmodified cells (-7.25 cells per day) ($P = 0.02$)
- HIV RNA became undetectable in one of four patients who could be evaluated

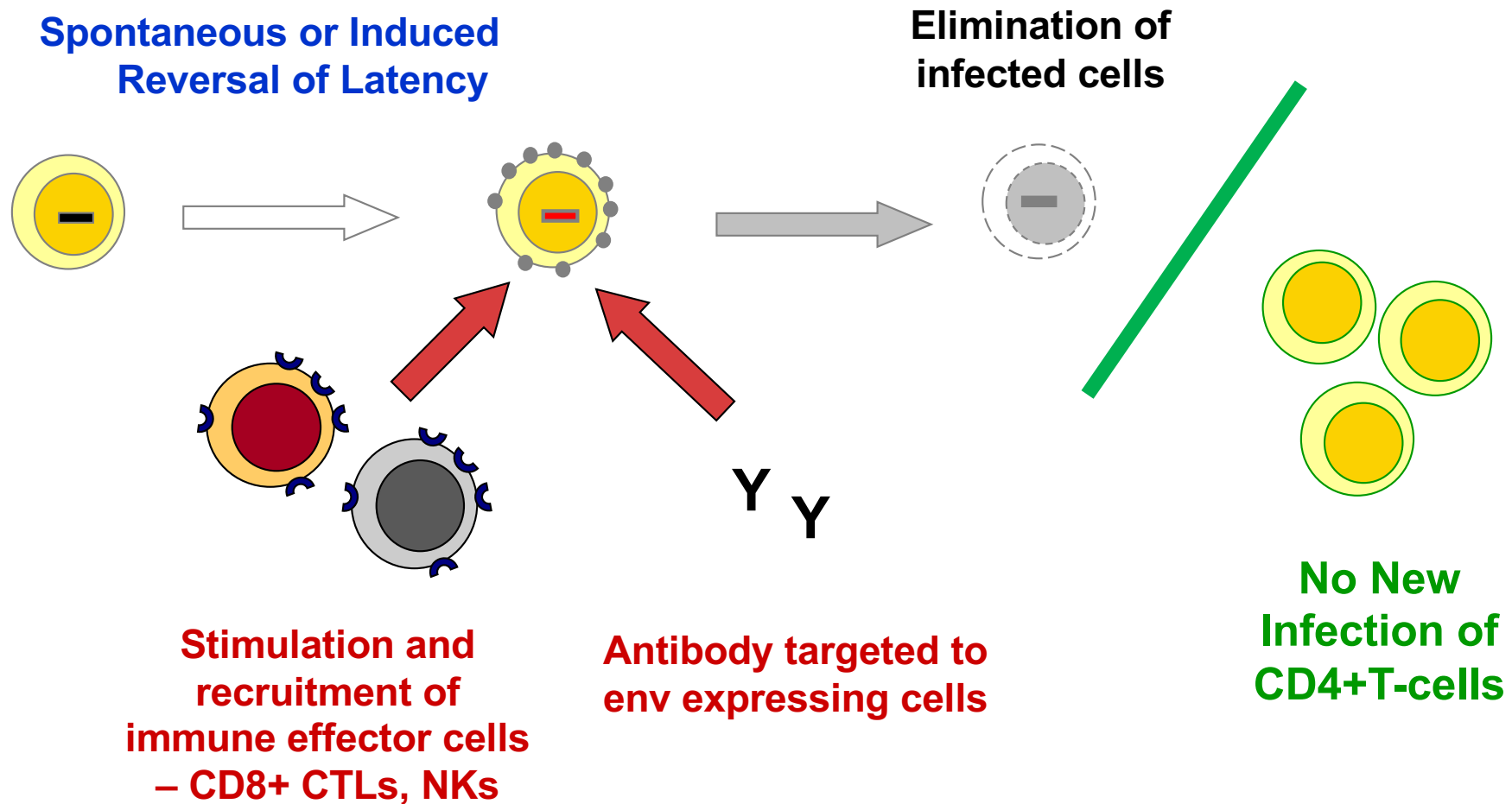


- Challenges moving forward:
 - Is cytoreductive therapy needed? Acceptable?
 - Is there X4 escape?
 - Scalability? Cost?

Which Cure Strategy?



“Kick and Kill” Strategy for HIV Cure



Modified from Romas Geleziunas

“Kick & Kill” Candidates

- Latency Reversing Agents (LRAs)
 - HDACi
 - **lack potency and killing as single agents**
 - PKC agonists
 - most potent activators but toxicity of concern
 - TLR agonists:
 - **activate HIV expression and immune control in SIV/macques**
- Natural and Engineered Antibodies
 - Broadly-neutralizing monoclonal antibodies (bnMAbs)
 - Can delay rebound and promote cell clearance in humans (3BNC117)
 - Resistance can rapidly develop (VRC01, 3BNC117)
 - **Effect in individuals on ART? (VRC01)**
 - Engineered bnMAb
 - Can prolong half-life and enhance Fc effector functions (e.g. PGT-151)
 - Bispecific Ab (anti-HIV/anti-host, e.g. CD3 or CD16)
 - Enhance effector function *ex vivo* and in animal models

Apologies, too many references to cite!

“Kill & Control” Candidates

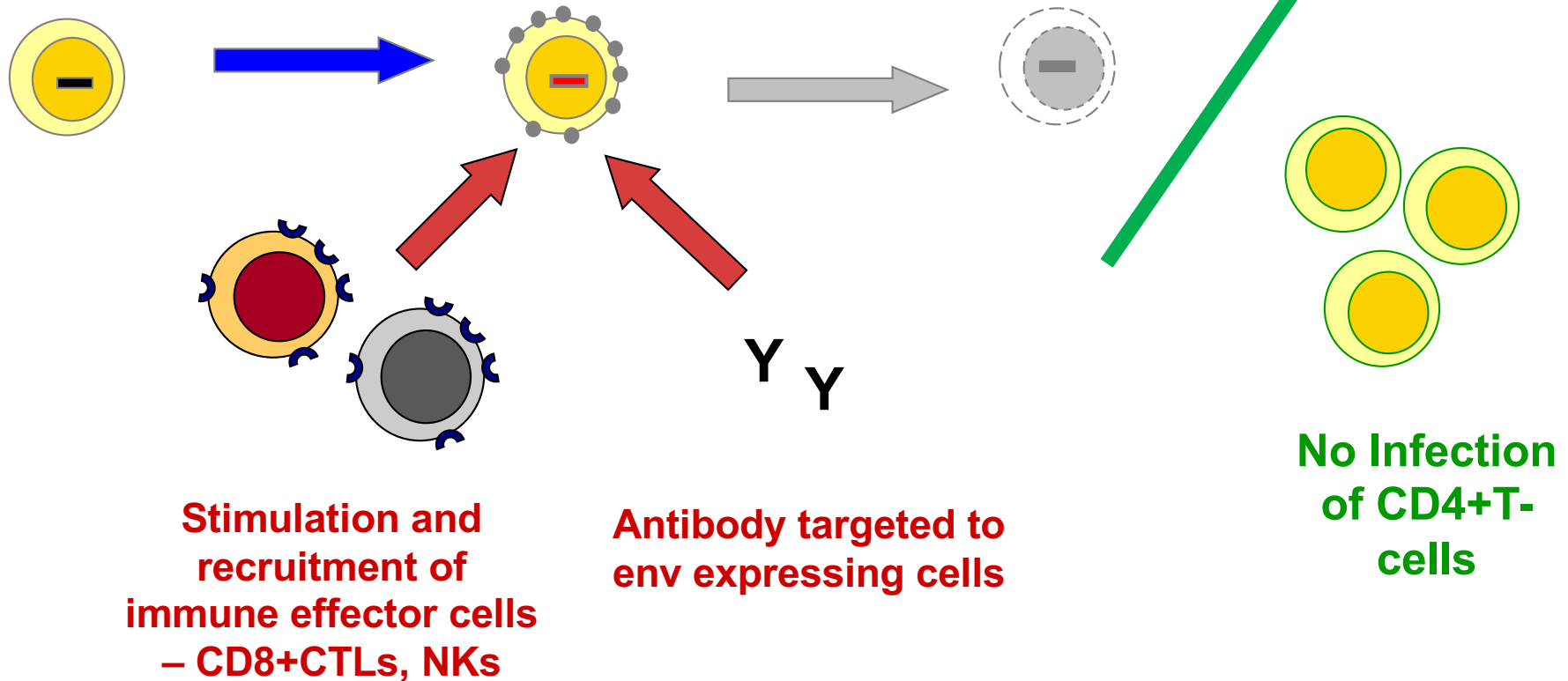
- Immune Checkpoint Blocking Antibodies
 - Major advance in cancer immunotherapy
 - Reverse immune exhaustion
 - Examples: Anti-PD-1/PD-L1, LAG-3, 2B4, CD160, TIM-3, others
- Cellular therapies
 - CD8+T-cells with chimeric antigen receptors
 - Activated NK cells
- Therapeutic Vaccines
 - Multiple approaches
 - CMV vector; VSV vector, **Ad26/MVA vectors**, Dendritic cell
 - Can induce broad CTL responses
 - Targeting conserved residues may be key

Apologies, too many references to cite!

“Kick/Kill” with HDACi?

Romidepsin (A5315)

Induced Reversal of Latency



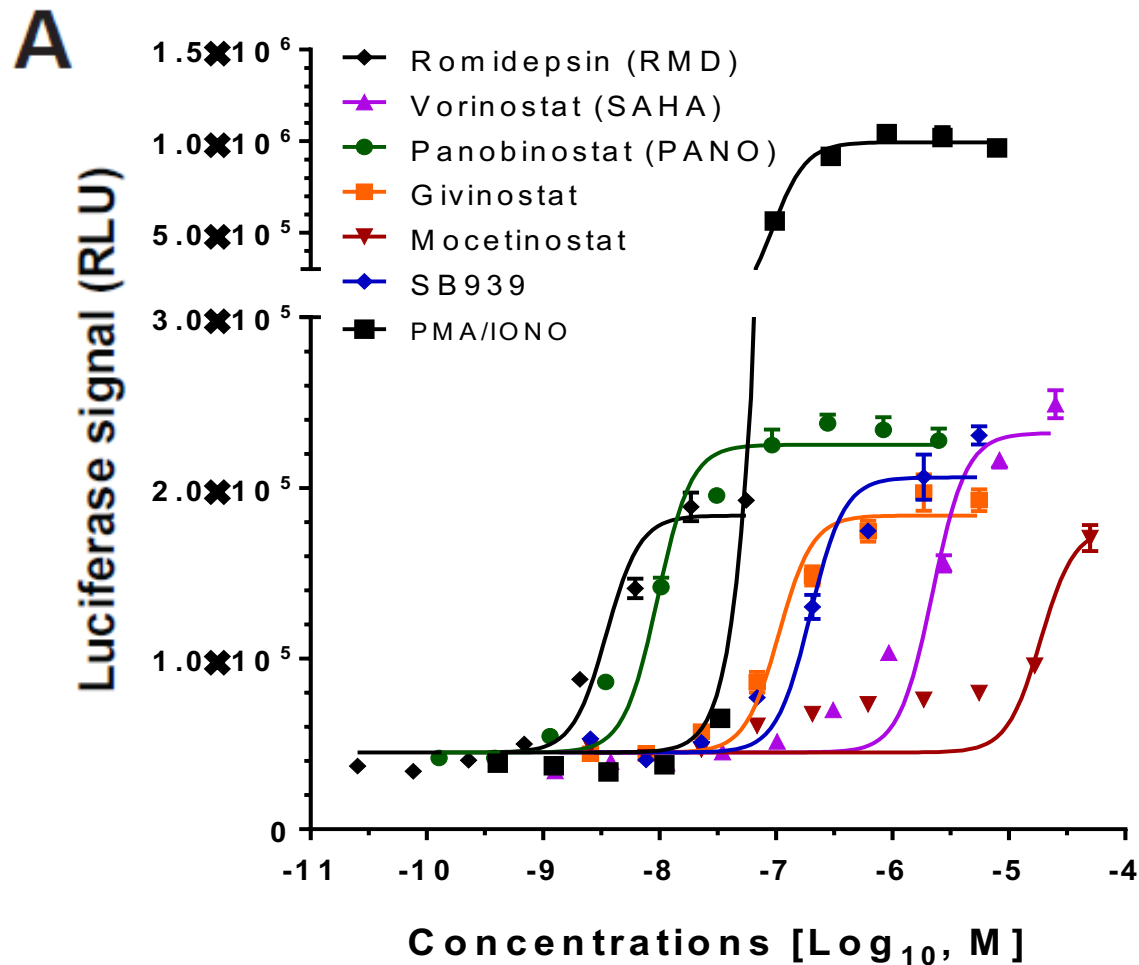
A5315: A Phase I/II Study of Romidepsin in HIV-Infected Adults with Suppressed Viremia on Antiretroviral Therapy to Assess Safety, Tolerability, and Activation of HIV-1 Expression

Deborah McMahon, MD, and John Mellors, MD

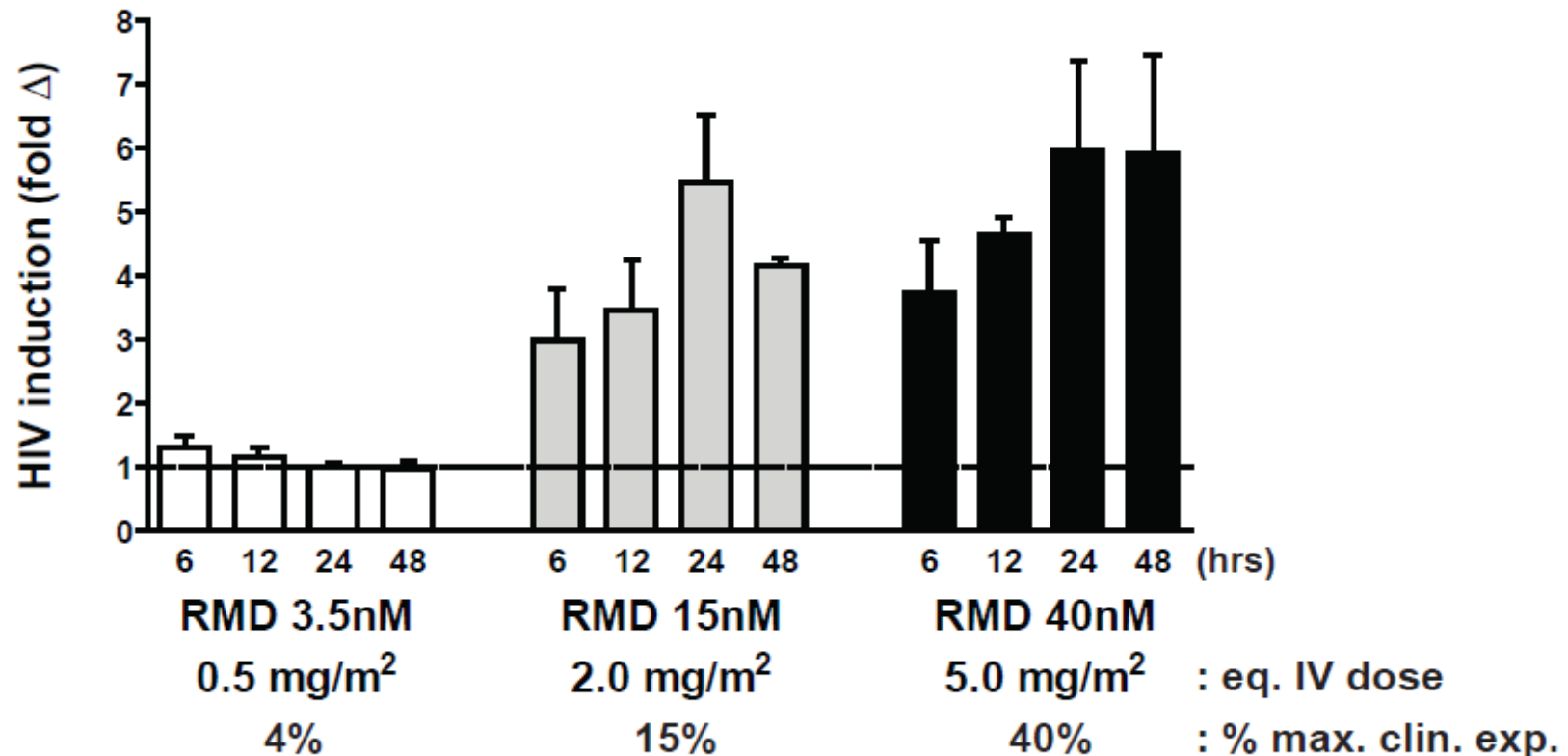
For the A5315 Team



Activation of HIV expression by HDACi in an in vitro latency model



RMD activates HIV RNA expression at concentrations below the levels achieved by dosing for lymphoma



A5315 Study Design and Completion

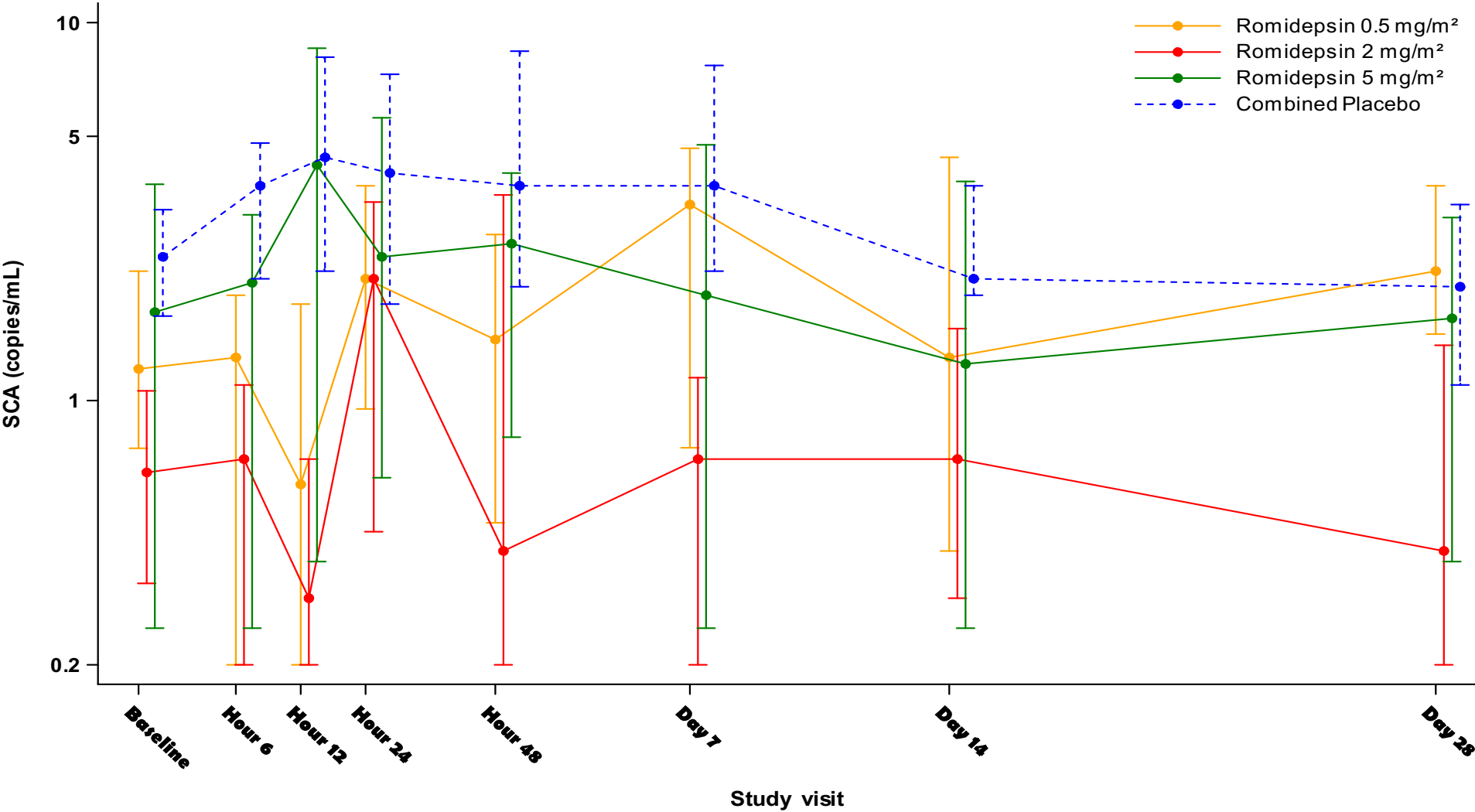
Study intervention: Participants randomized 4:1 to receive i.v. RMD (12 participants/cohort) or placebo (0.9% saline) (3 participants/cohort).

Cohort 1: 12 participants (0.5 mg/m² RMD in 0.9% saline) - completed

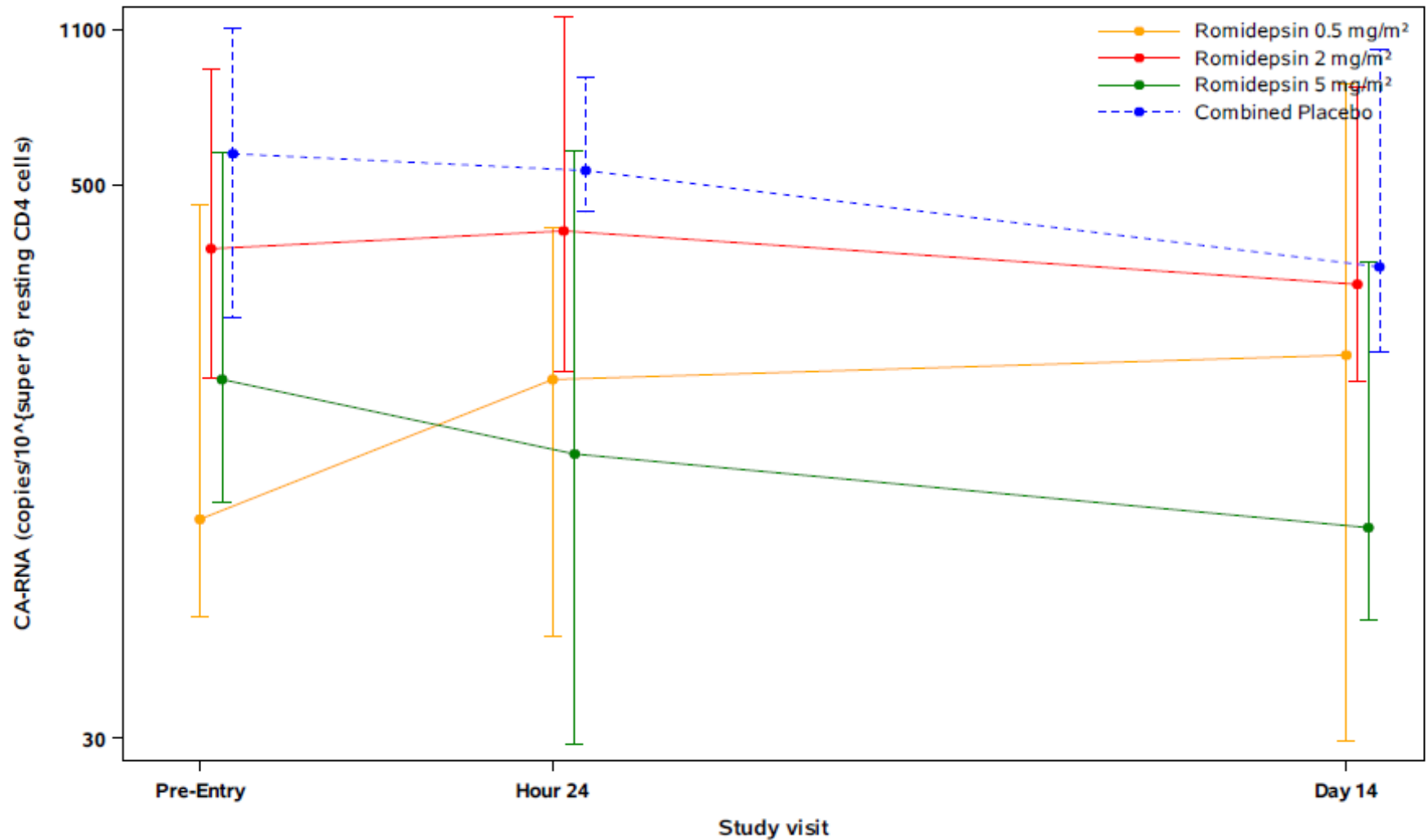
Cohort 2: 12 participants (2 mg/m² RMD in 0.9% saline) - completed

Cohort 3: 12 participants (5 mg/m² RMD in 0.9% saline) - completed

Viremia Measured by Single Copy Assay (Median) by Dose (0.5mg/m², 2mg/m², 5mg/m²)



Median (Q1, Q-3) CA-RNA copies/ 10^6 resting CD4+ cells over time (by dose)



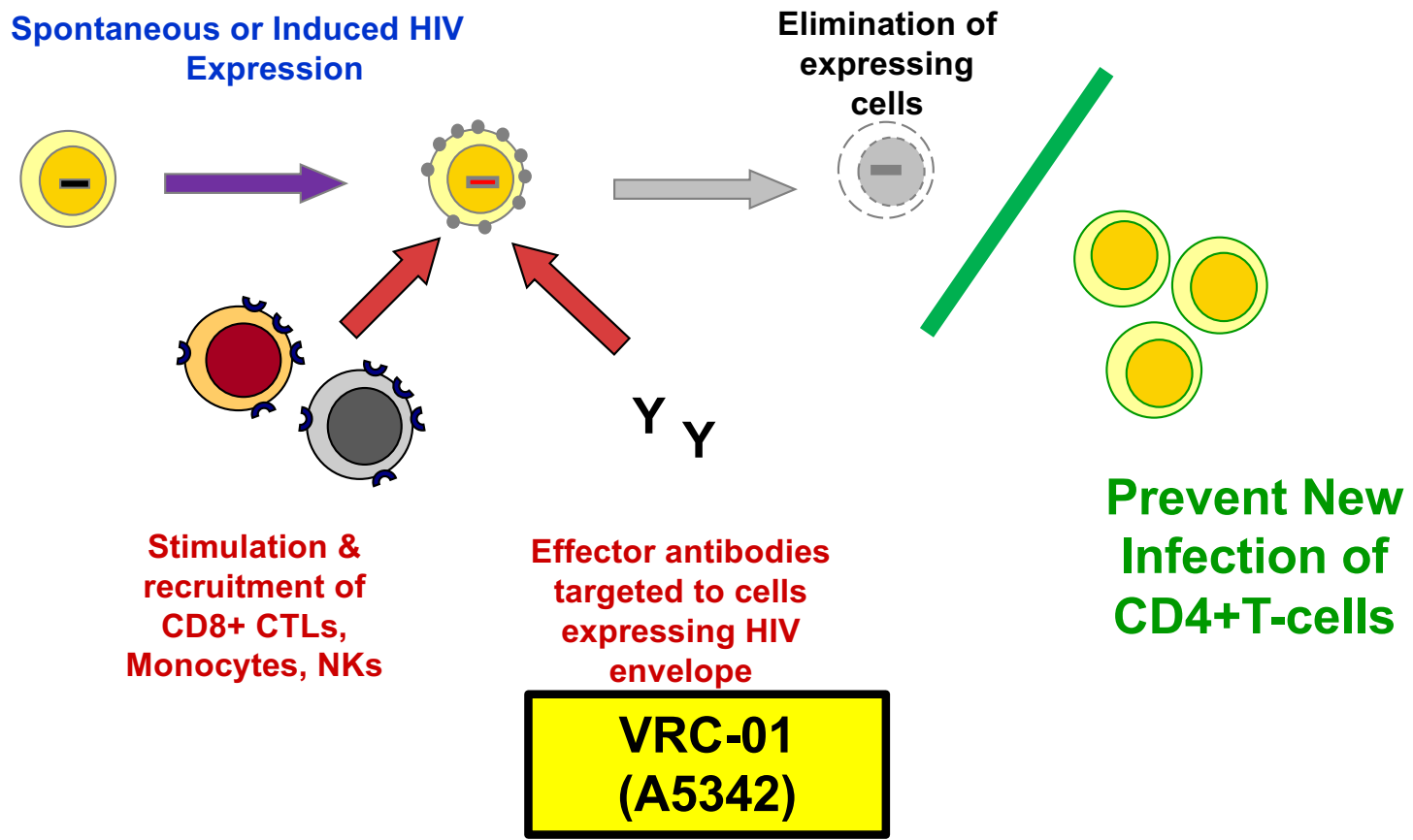
Romidepsin Concentrations ng/mL

Time Post-Infusion	Romidepsin Dose		
	0.5 mg/m ²	2 mg/m ²	5 mg/m ²
Hour 4 (Q1, Q3)	12 (6.6, 16.7)	75.2 (54.1, 84.0)	89 (53.3, 127.5)
Hour 6 (Q1,Q3)	3.2 (-,-)	2.7 (1.7, 4.2)	2.6 (2.0, 5.0)

A5315 Summary

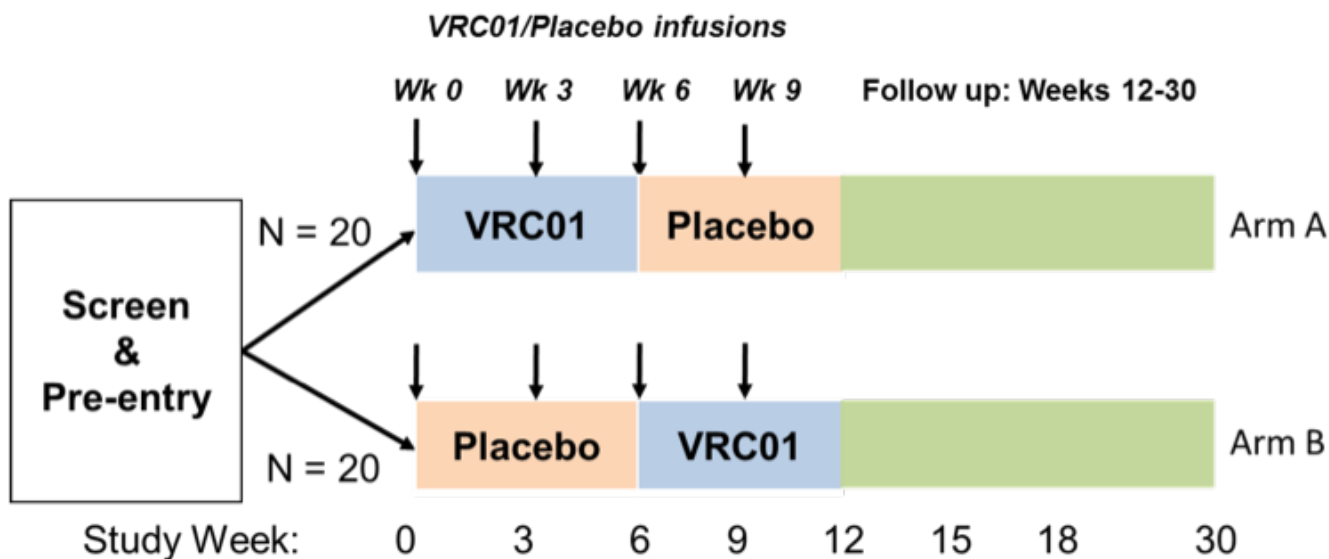
- Single dose RMD administered at doses below MTD was safe and well-tolerated
- No increase in viremia post-infusion noted as measured by SCA at average of hrs 24 and 48
- No change in HIV CA-RNA, CA-DNA in resting CD4⁺ cells pre-infusion to Hr 24
- No significant increases noted in any virologic measures in single dose cohorts compared to combined placebo
- RMD exposure dose-dependent
- No apparent effect on histone acetylation
- Multiple RMD dosing Cohort 4 underway

“Antibody-Mediated Kill”: Human Study



A5342/VRC01 Study

- Double-blind, randomized, placebo-controlled, Phase I study
- 40 participants (20 per arm)
- VRC01 40 mg/kg IV at Day 0 & 21 (Arm A) or Day 42 & 63 (Arm B)



Summary of Virologic Outcomes

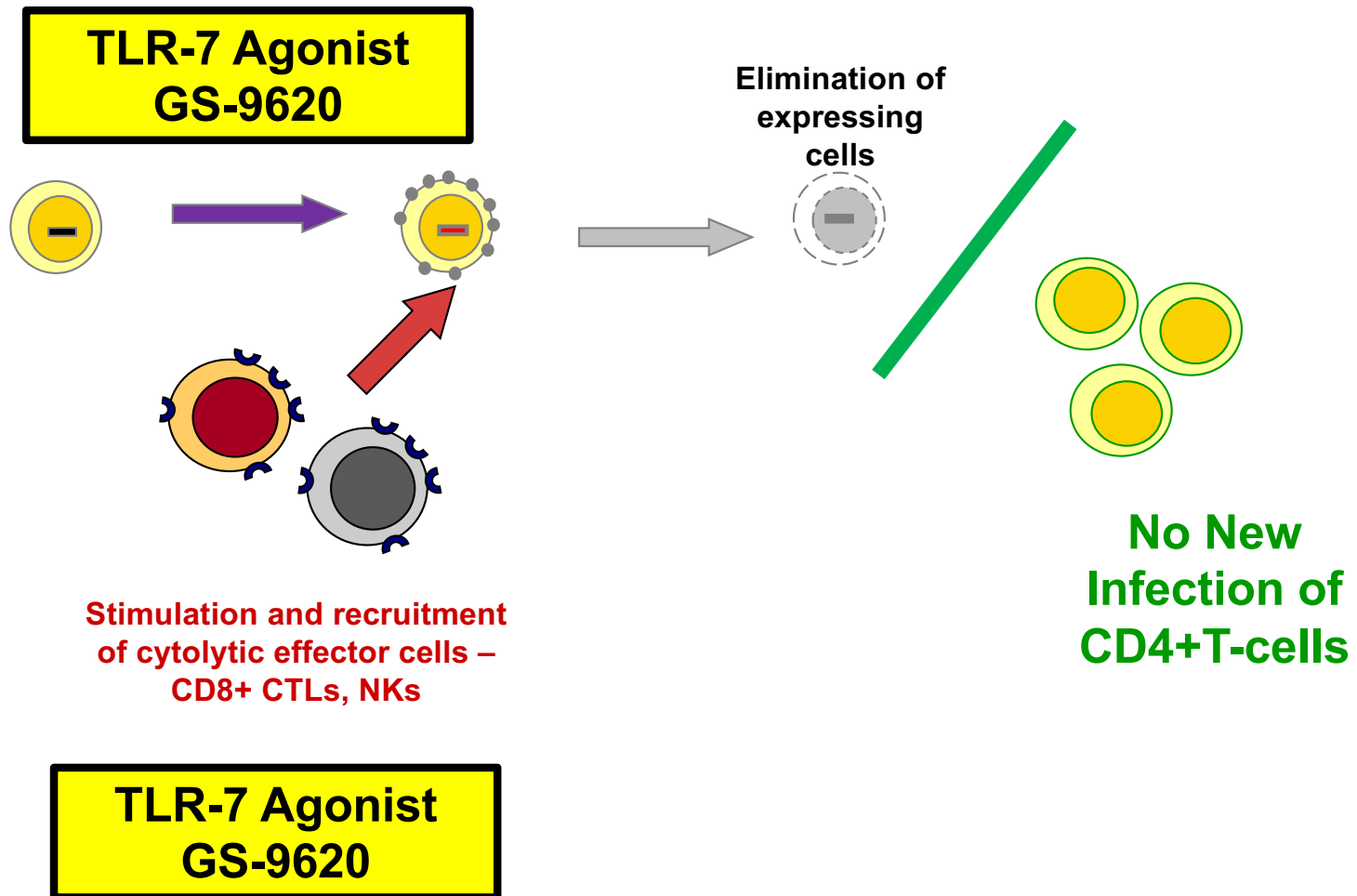
Parameter Median (Q1, Q3)	Arm A	Arm B	p-value*	Arms A and B Combined		Change from Pre- to Post- VRC01	p-value**
	Change from baseline to Week 6			Pre-VRC01 values	Post-VRC01 values		
Cell-associated HIV RNA/DNA ratio^	1.12 (0.92, 2.15)	0.83 (0.57, 2.37)	0.16	0.04 (0.02 0.08)	0.05 (0.02, 0.08)	1.24 (0.61, 2.15)	0.29
Cell-associated HIV RNA (log ₁₀ cps/10 ⁶ CD4 cells)	0.08 (-0.23, 0.32)	-0.08 (-0.26, 0.29)	0.39	1.55 (0.99, 1.99)	1.48 (0.99, 2.10)	0.09 (-0.23, 0.32)	0.64
Cell-associated HIV DNA (log ₁₀ cps/10 ⁶ CD4 cells)	-0.06 (-0.13, 0.06)	-0.01 (-0.08, 0.13)	0.30	2.93 (2.43, 3.15)	2.92 (2.51, 3.11)	-0.05 (-0.12, 0.06)	0.19
Stimulated Virus Production from total CD4+T-cells (log ₁₀ cps/ml)	-0.13 (-0.51, 0.92)	0.12 (-0.52, 0.30)	0.91	2.99 (2.06, 3.37)	2.66 (2.28, 3.41)	-0.10 (-0.51, 0.44)	0.85
	Week 6		p-value***				p-value****
Plasma HIV RNA ≥1 cp/ml by single copy assay (%)	8/19 (42%)	7/19 (37%)	1.0	16/38 (42%)	14/38 (37%)		0.59

Riddler, et al. CROI 2017

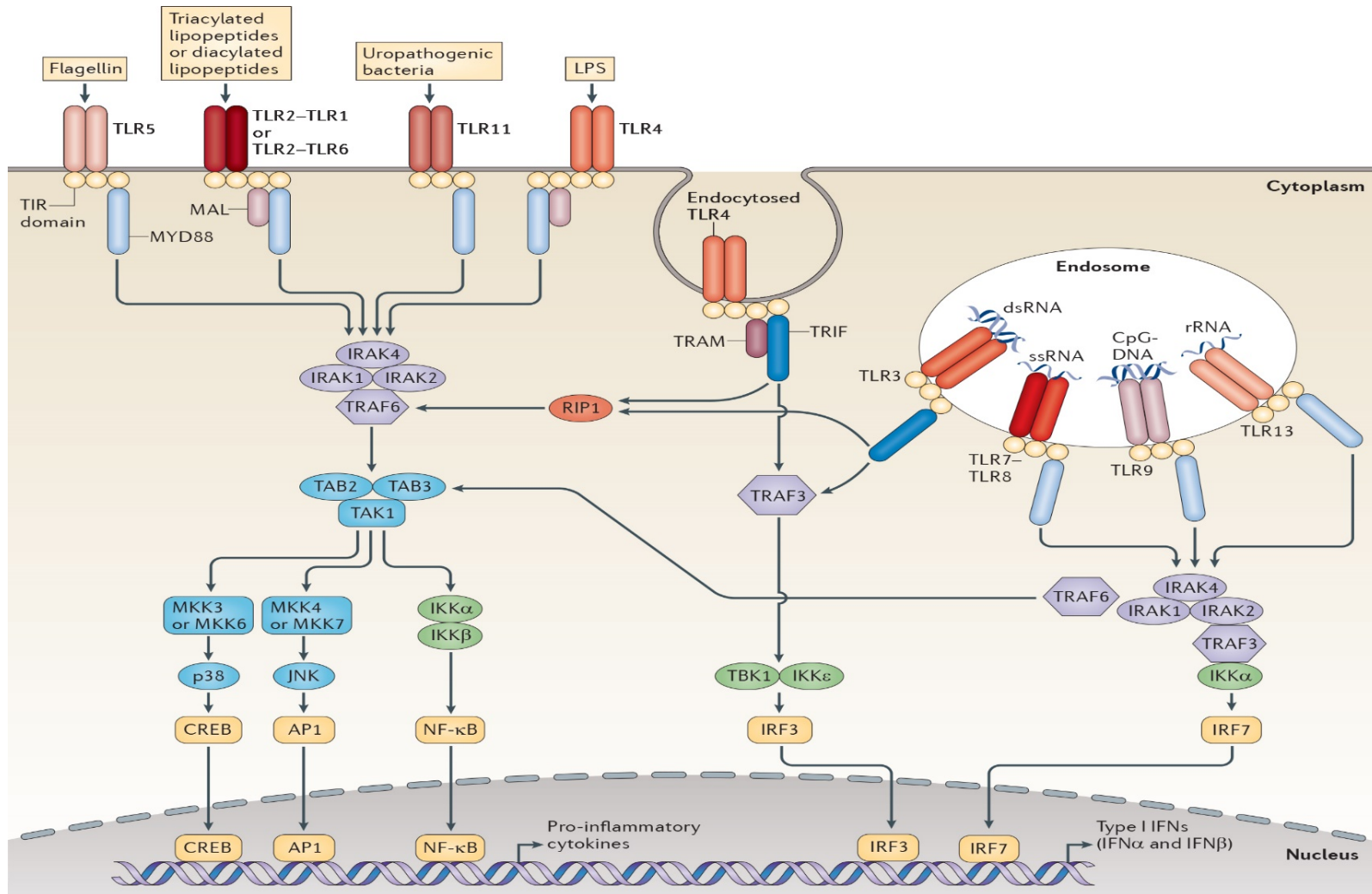
A5342 Conclusions

- In individuals with chronic ART-suppressed HIV infection, VRC01 infusions were **safe** and well tolerated.
- Two high-dose infusions of VRC01 did **not** affect virologic outcomes including:
 - Residual plasma viremia
 - Cell-associated HIV RNA/DNA levels
 - Total stimulated virus production from CD4+T-cells
- Potential mechanisms being evaluated to explain the lack of response include
 - viral envelope resistance to VRC01
 - inherent inability of VRC01 to clear virus or env-expressing cells
 - poor penetration of VRC01 to sites of virus expression

“Kick & Kill”: Macaque → Human Studies

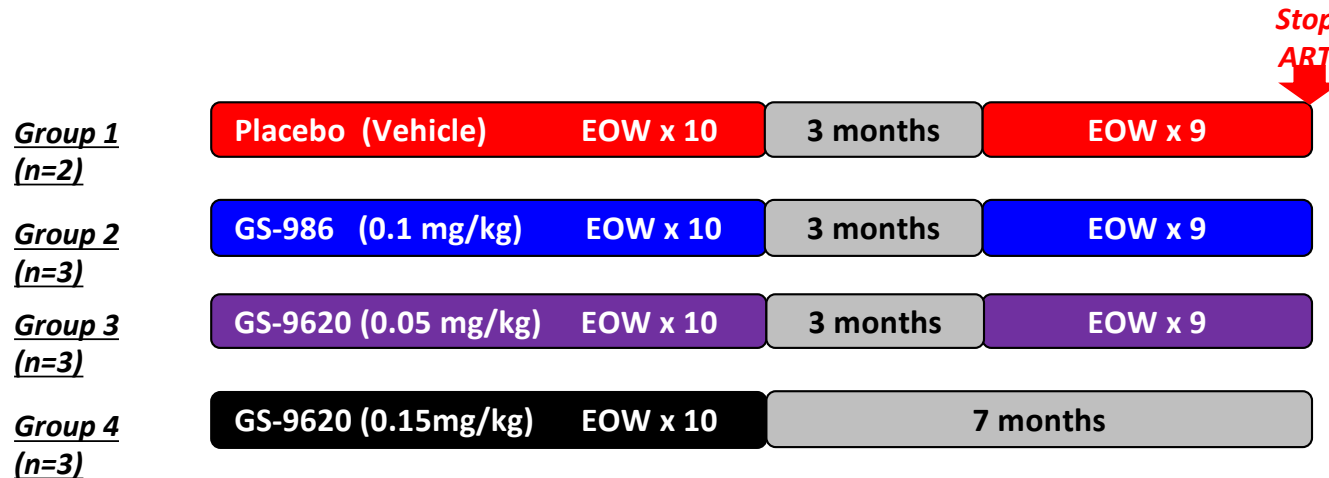


TLR Signalling

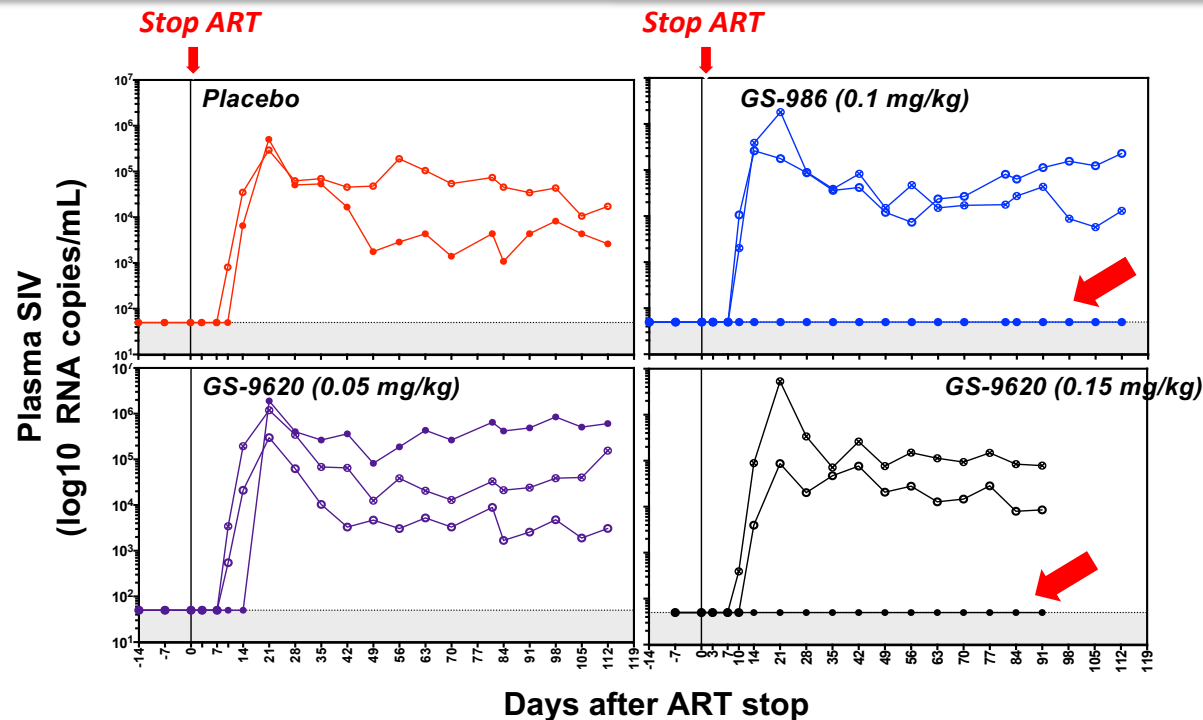


TLR7 Agonists in SIV+ Rhesus on ART– Study #2

- 11 Rhesus monkeys (A*01, B*08, B*17 neg.), SIVmac251 IR infection
- ART - initiated day 65 post-infection (TFV, FTC, DTG s.c. q.d.)
- Day 467 post-infection initiate TLR7 agonist treatment
- Endpoints: change in plasma viral RNA, monitor immune activation, perturbation of the reservoir and viral rebound after stopping ART



Plasma SIV RNA Rebound after Stopping ART



- 2 of 9 animals treated with TLR7 agonists have undetectable plasma virus up to 3-4 months off ART
- Same 2 animals with no inducible virus in PBMC and LN cultures

Phase I/II trial of GS-9620 in HIV-infection

Design:

- 4 escalating dose cohorts
 - 1 mg, 2 mg, 4 mg, 6 mg every 2 weeks for 6 doses
- Placebo-controlled, randomized, double-blinded (6 active, 2 placebo per cohort)

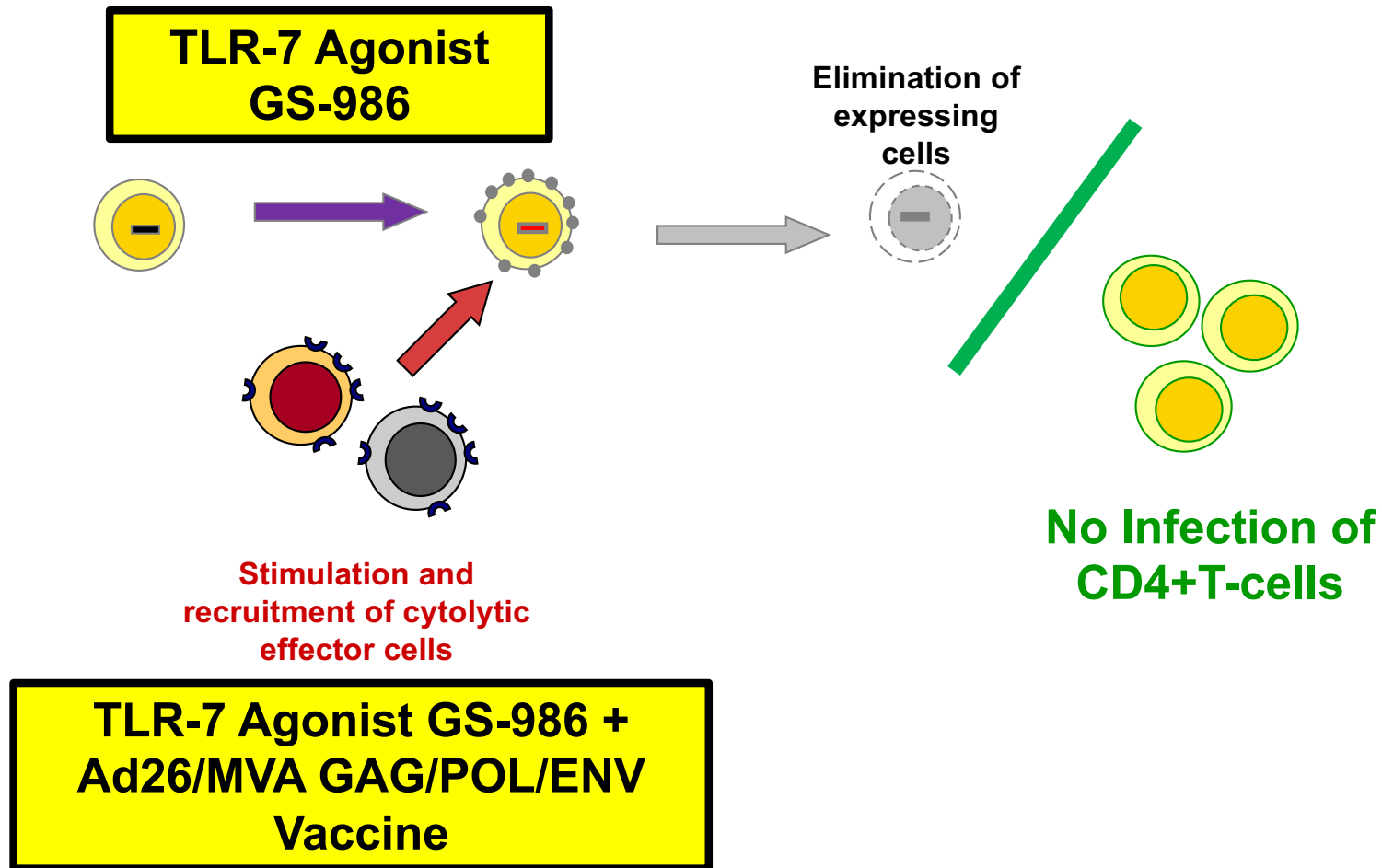
Study Population:

- HIV-infected adults (n=24)
- Virologically suppressed ≥ 12 months on ART

Study Monitoring:

- Close follow-up – VL 2-3x/w
- Repeat dosing only if VL <50 copies/mL
- Safety review prior to initiation of each cohort

“Kick and Kill”: Macaque → Human Studies

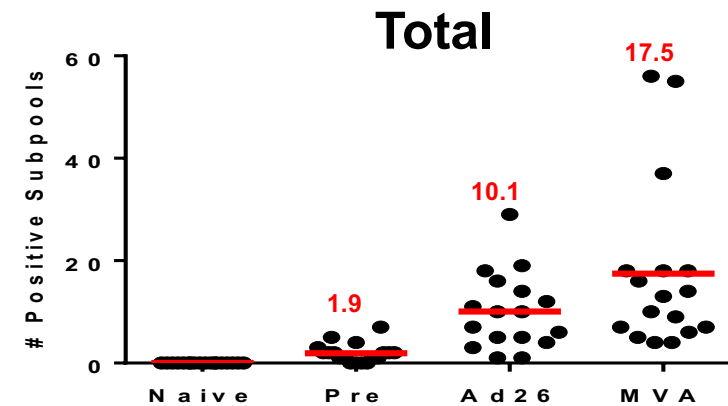
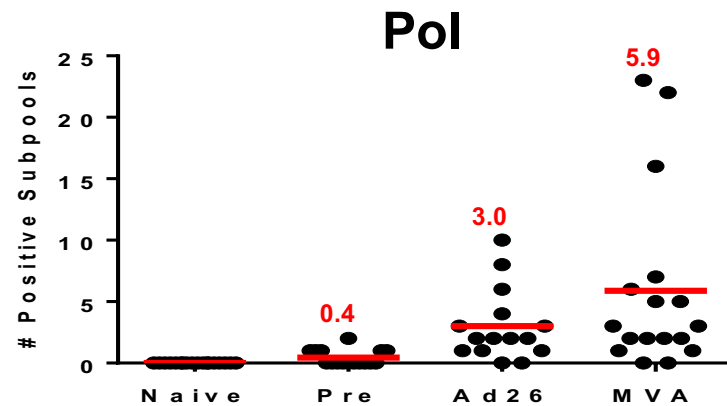
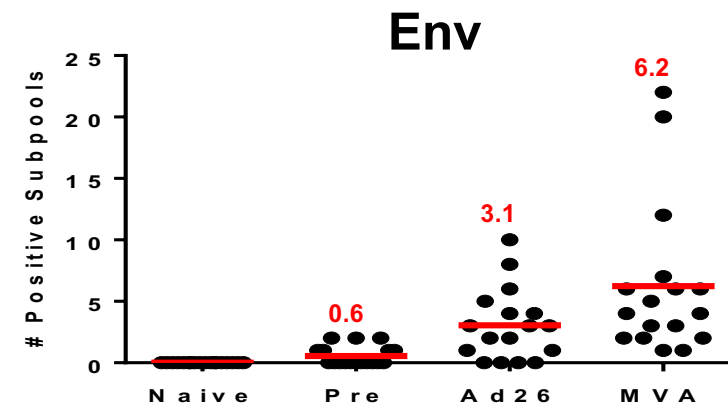
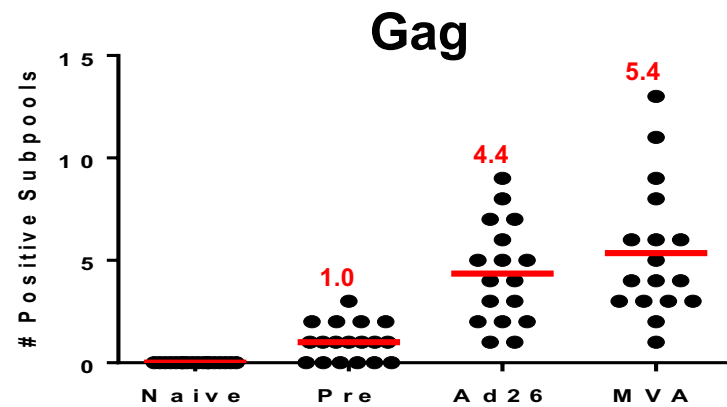


Ad26/MVA Therapeutic Vaccine Study in ART-Suppressed, SIV-Infected Rhesus Monkeys

- 36 rhesus monkeys infected i.r. with SIVmac251
- Preformulated daily ART initiated on day 7 s.q. (TDF, FTC, DTG)
 - Group 1: Ad26/MVA Alone (N=9)
 - Group 2: Ad26/MVA + TLR7 Agonist GS-986 (N=9)
 - Group 3: TLR7 Agonist GS-986 Alone (N=9)
 - Group 4: Sham (N=9)
- 2 x Ad26-SIVsmE543 Env/Gag/Pol (3×10^{10} vp i.m.) at weeks 24, 36
- 2 x MVA-SIVsmE543 Env/Gag/Pol (10^8 pfu i.m.) at weeks 48, 60
- 10 x GS-986 (0.3 mg/kg p.o.) at weeks 50-70 (every 2 weeks)
- ART discontinued at week 72

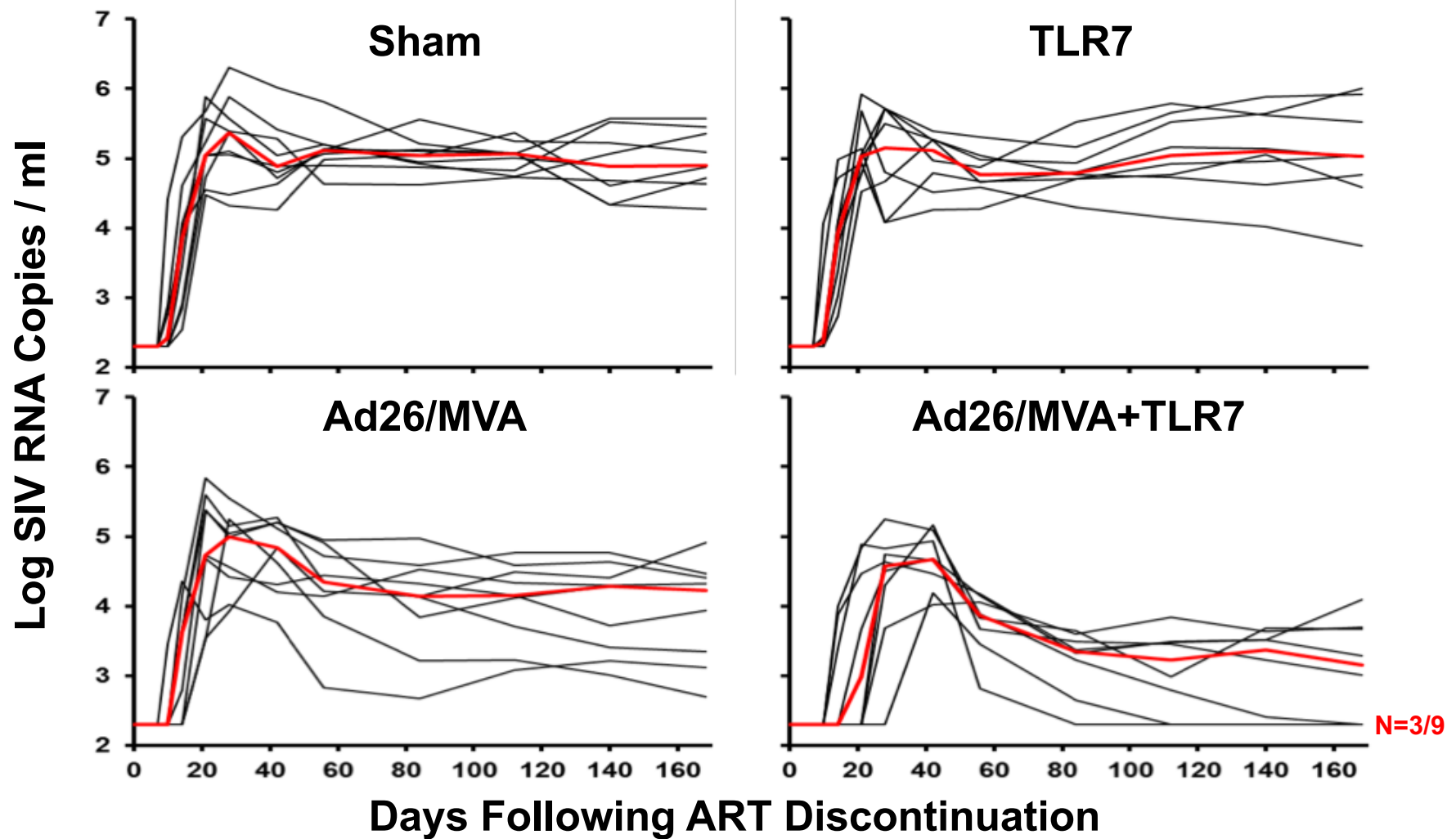


9.2-Fold Expansion of Cellular Immune Breadth by Ad26/MVA Vaccination

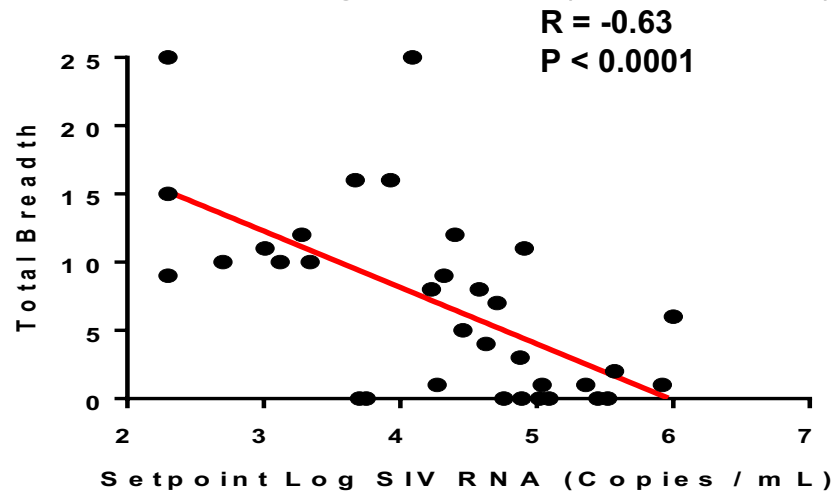
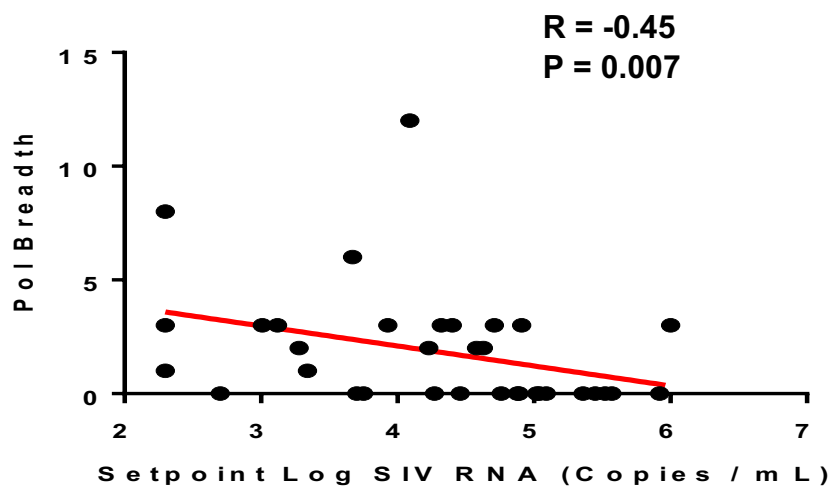
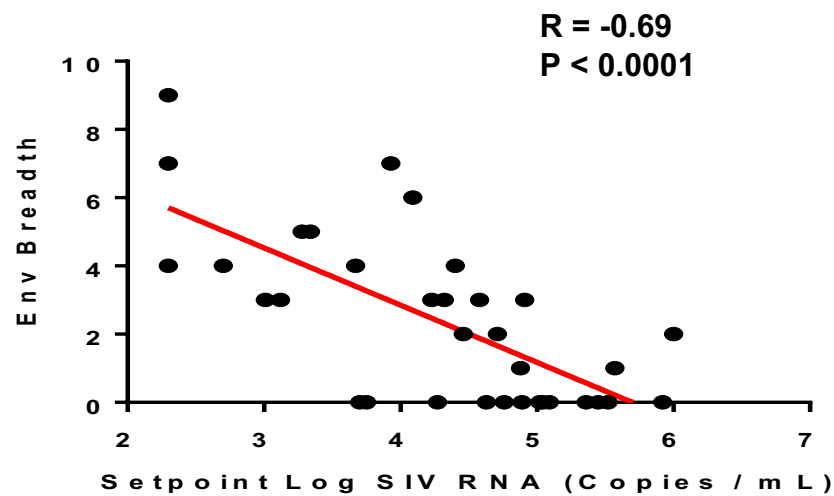
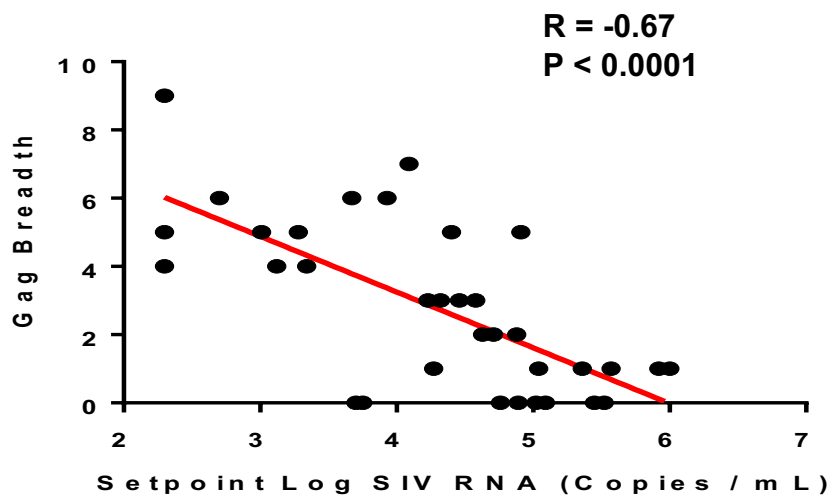


9.2-fold expansion of breadth

SIV RNA Following ART Discontinuation



Setpoint Viral Load Correlates with Cellular Immune Breadth at Time of ART Discontinuation



How does the future look for HIV cure?

- The bar is high
 - Especially for HIV eradication (sterilizing cure) and for one effective in all HIV positive persons
- There are still fundamental knowledge gaps
 - Brain reservoirs – final frontier!
 - Immunologic correlates of viral control
- More cures – control of viremia off ART - will come!
 - In specific populations first
 - **early ART + TLR agonist + vaccine or bnmAb?**
- There are always unrealistic optimists and skeptics
 - Remember, 1 pill a day to treat HIV was a once fantasy!

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Study Participants

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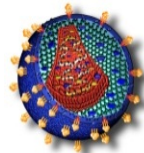


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Questions?